THE NORMOBARIC OXYGEN PARADOX : FROM BREATH-HOLD DIVING TO THE PATIENT'S BED

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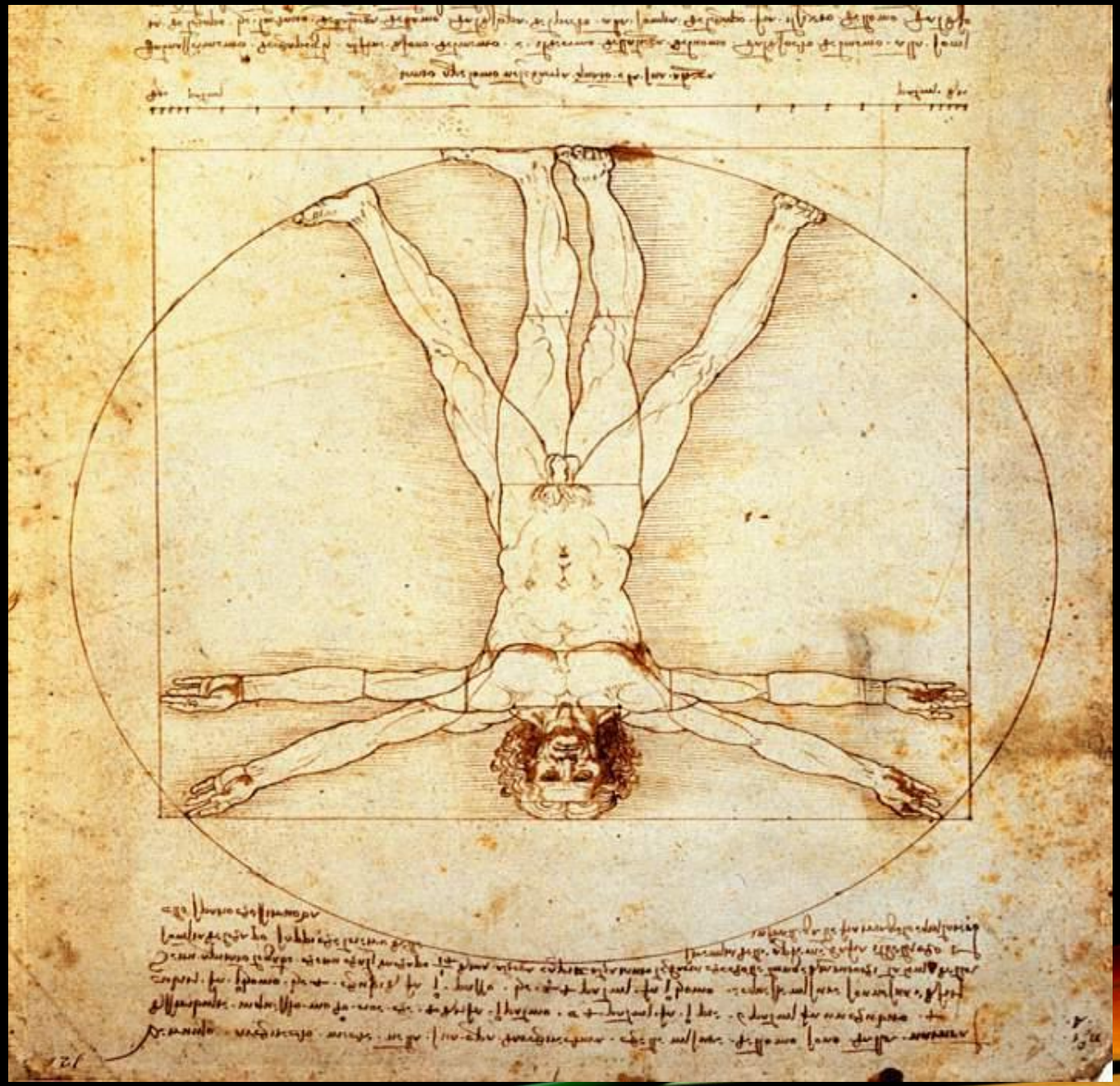
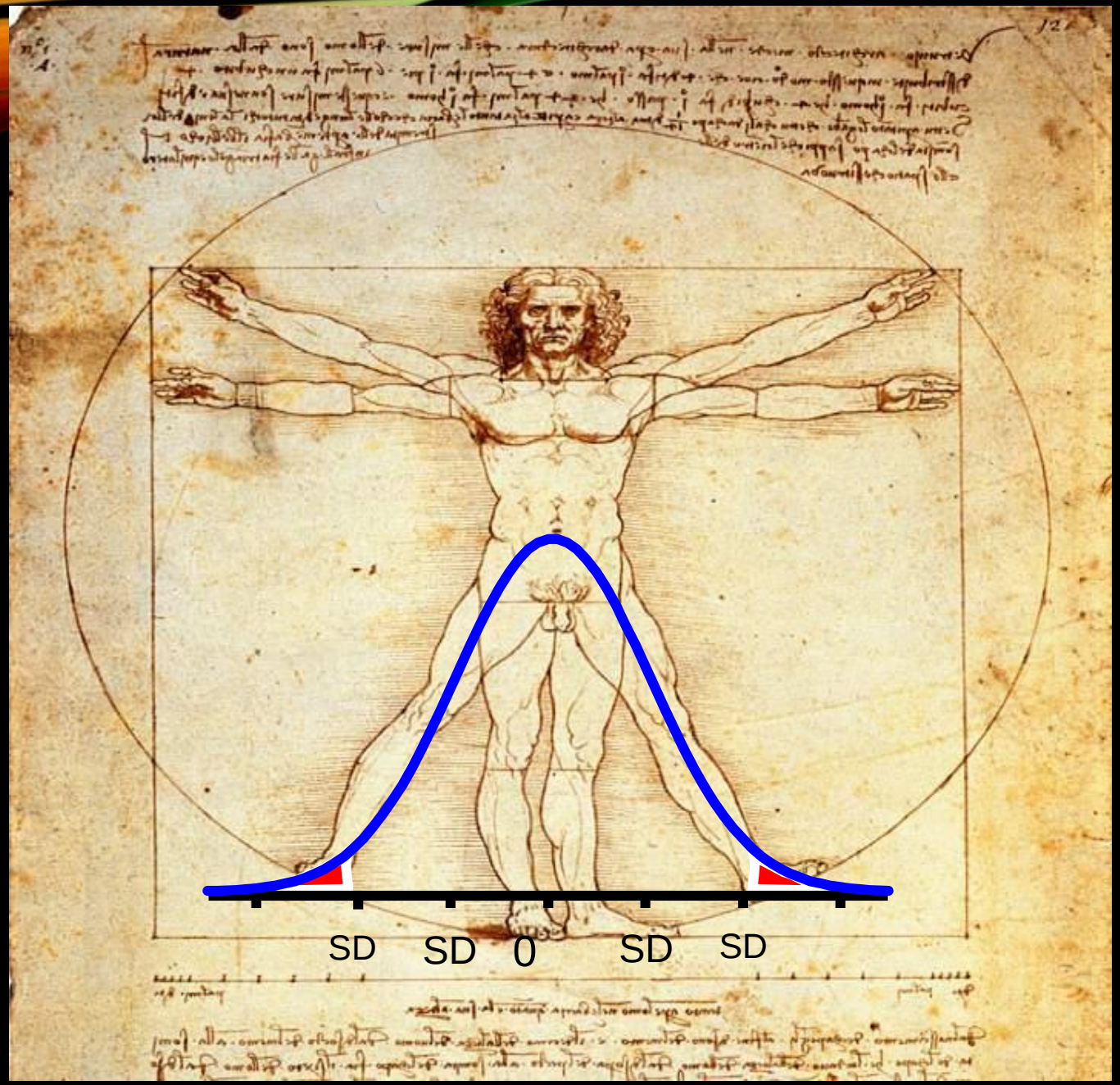
Disclaimer

- I declare **no real or potential conflict of interest**.

- Any views or opinions presented in this presentation are solely those of the author and do not necessarily represent those of any organization that author belongs to.

OXYGEN SENSING FOOLS JANUS

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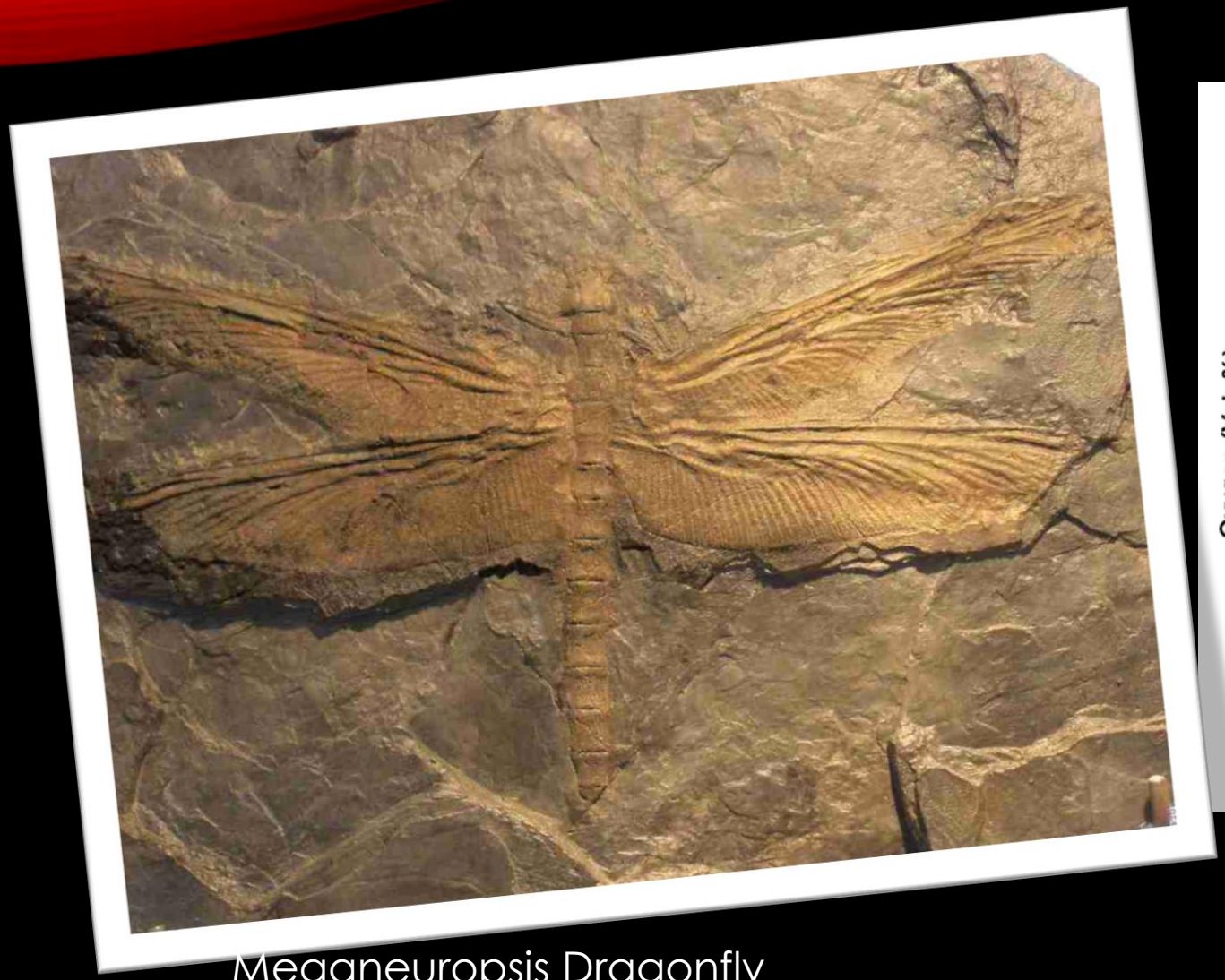
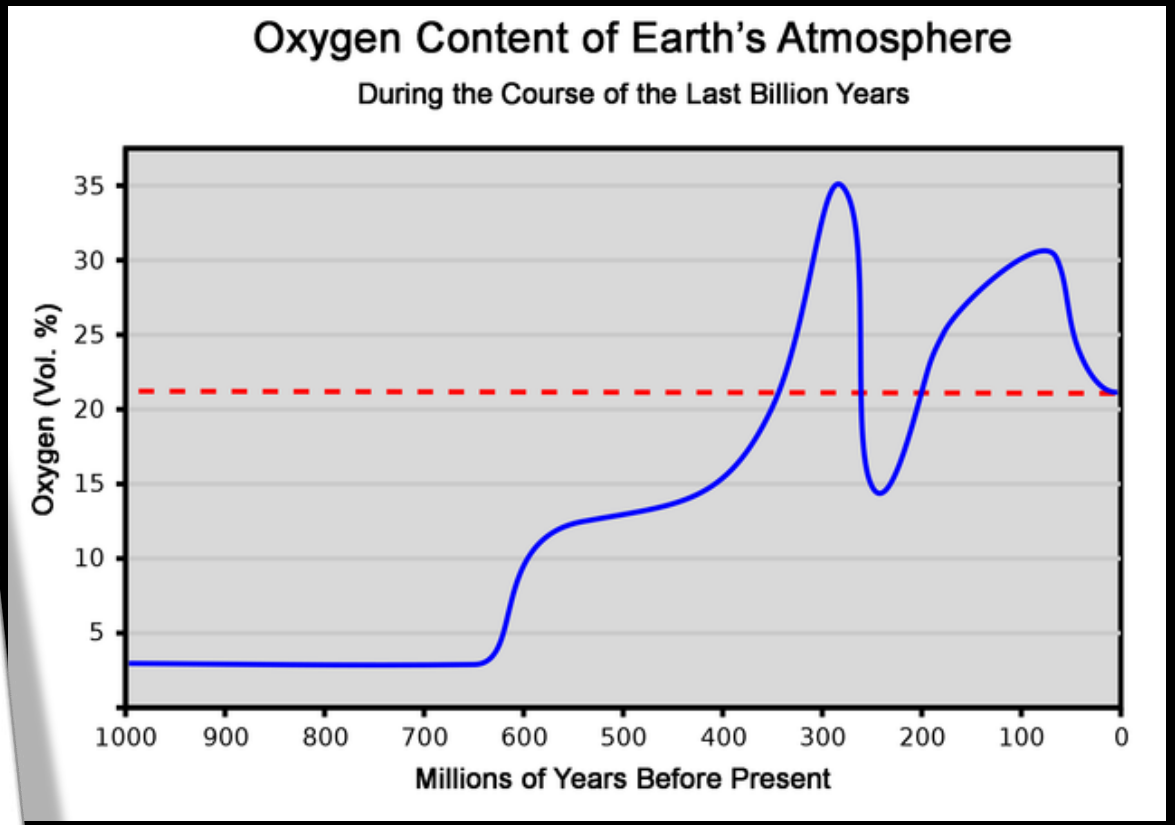
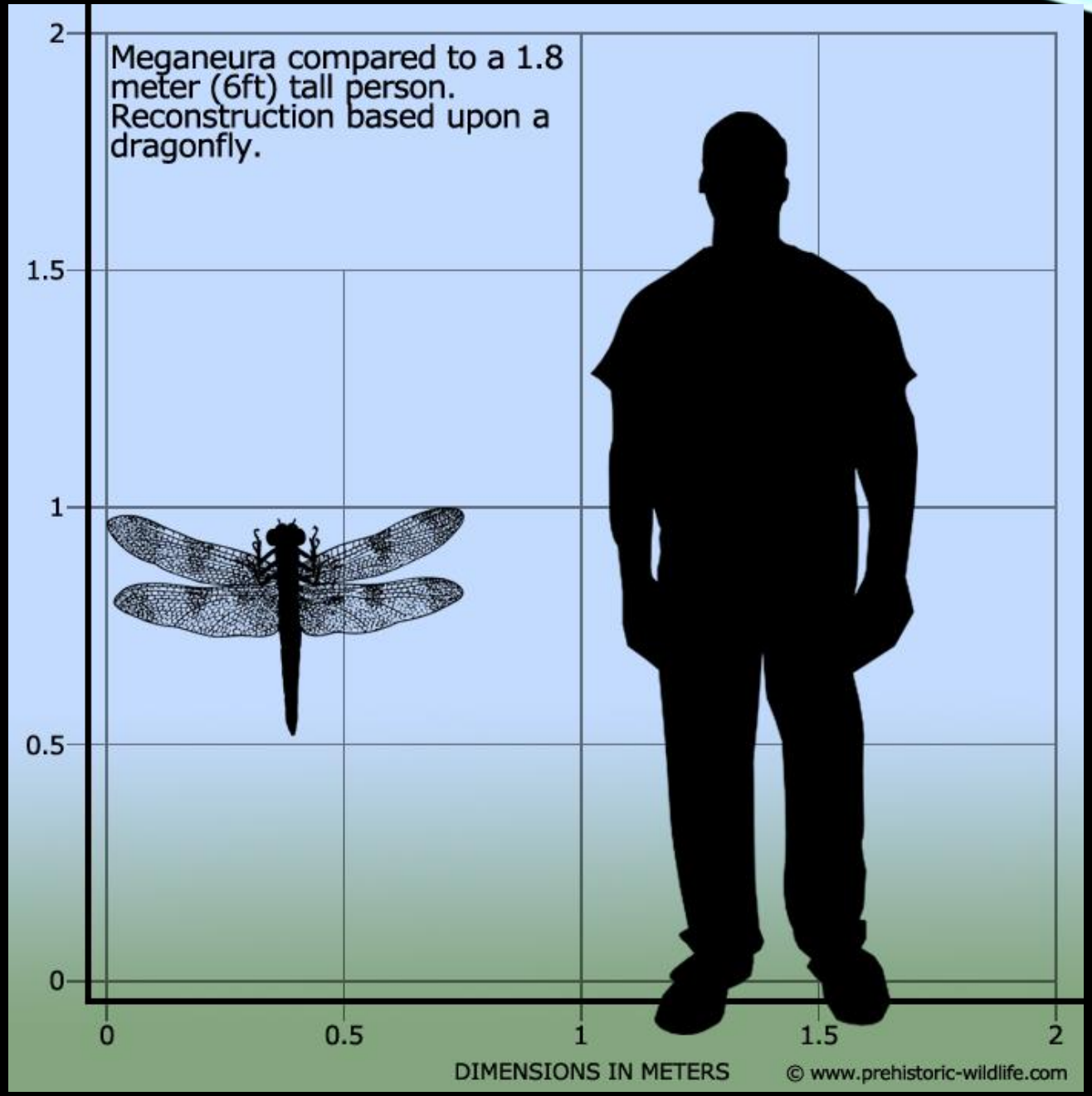


Meganeuropsis Dragonfly



GIGANTISM=PROTECTION

During Carboniferus Oxygen content in the atmosphere was Arond 28%



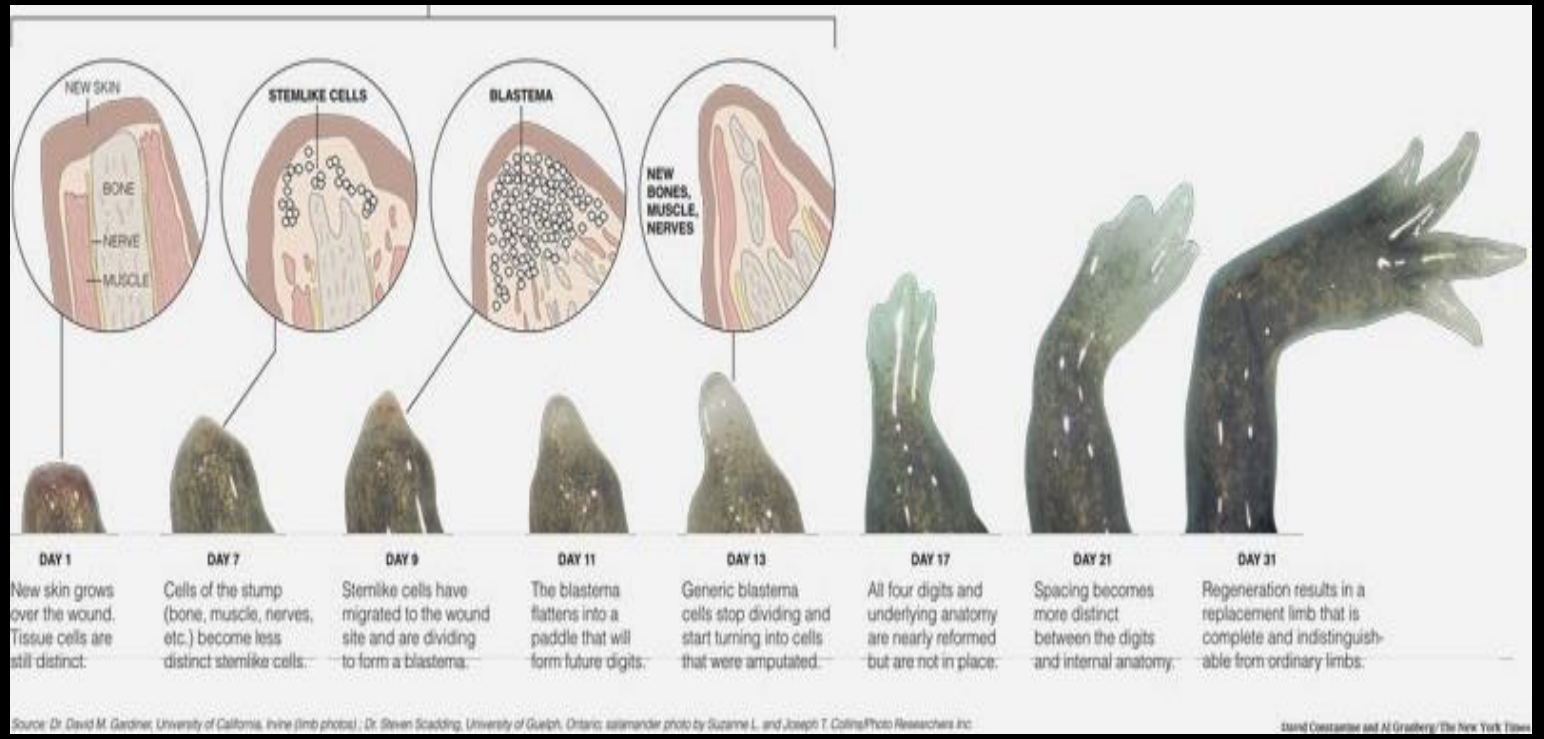
REJUVINATION RECONSTRUCTION

WE NEED BASICALLY 3 INGREDIENTS

Trigger (deltas- Hif)

Target (Stem Cells)

Supporting environment (Oxygenated tissue)



Am J Physiol Heart Circ Physiol 290: H1378–H1386, 2006.
First published November 18, 2005; doi:10.1152/ajpheart.00888.2005.

CALL FOR PAPERS | *Regulation and Function of Stem Cells in the Cardiovascular System*

Stem cell mobilization by hyperbaric oxygen

Stephen R. Thom,[1,2] Veena M. Bhopale,[1] Omaida C. Velazquez,[3] Lee J. Goldstein,[3] Lynne H. Thom,[1] and Donald G. Buerk[4]

[1]*Institute for Environmental Medicine and Departments of* [2]*Emergency Medicine,* [3]*Surgery, and* [4]*Physiology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania*

Submitted 19 August 2005; accepted in final form 7 November 2005

Thom, Stephen R., Veena M. Bhopale, Omaida C. Velazquez, Lee J. Goldstein, Lynne H. Thom, and Donald G. Buerk. Stem cell mobilization by hyperbaric oxygen. *Am J Physiol Heart Circ Physiol* 290: H1378–H1386, 2006. First published November 18, 2005; doi:10.1152/ajpheart.00888.2005.—We hypothesized that exposure to hyperbaric oxygen (HBO_2) would mobilize stem/progenitor cells from the bone marrow by a nitric oxide (·NO) -dependent mechanism. The population of $CD34^+$ cells in the peripheral circulation of humans doubled in response to a single exposure to 2.0 atmospheres absolute (ATA) O_2 for 2 h. Over a course of 20 treatments, circulating $CD34^+$ cells increased eightfold, although the overall circulating white cell count was not significantly increased. The number of colony-forming cells (CFCs) increased from 16 ± 2 to 26 ± 3 CFCs/100,000 monocytes plated. Elevations in CFCs were entirely due to the $CD34^+$ subpopulation, but increased cell growth only occurred in samples obtained immediately posttreatment. A high proportion of progeny cells express receptors for vascular endothelial growth factor-2 and for stromal-derived growth factor. In mice, HBO_2 increased circulating stem cell factor by 50%, increased the number of circulating cells expressing stem cell antigen-1 and CD34 by 3.4-fold, and doubled the number of CFCs. Bone marrow ·NO concentration increased by 1,008 ± 255 nM in association with HBO_2. Stem cell mobilization did not occur in knockout mice lacking genes for endothelial ·NO synthase. Moreover, pretreatment of wild-type mice with a ·NO synthase inhibitor prevented the HBO_2-induced elevation in stem cell factor and circulating stem cells. We conclude that HBO_2 mobilizes stem/progenitor cells by stimulating ·NO synthesis.

nitric oxide; CD34; CD133; CXCR4; cKit; colony-forming cells; progenitor cells

28, 32). Hematopoietic SPCs are typically obtained for the purpose of bone marrow transplantation by administration of chemotherapeutic agents and growth factors (36). Utilizing these agents to obtain autologous SPCs for treating disorders such as organ and limb ischemia, and refractory wounds, has been considered, but application is thwarted because of risks such as acute arterial thrombosis, angina, sepsis, and death (7, 20, 21, 27, 29, 30, 36).

Nitric oxide (·NO) plays a key role in triggering SPC mobilization from the bone marrow via release of the stem cell active cytokine, cKit ligand (stem cell factor, SCF) (1, 8). Because HBO_2 can activate ·NO synthase in different tissues, we hypothesized that exposure to HBO_2 may stimulate SPC mobilization to the peripheral circulation (33, 34). In a murine model, we found HBO_2 augments SPC mobilization and recruitment to ischemic wounds and hastens ischemic wound healing (Goldstein LJ, Gallagher K, Baireddy V, Bauer SM, Bauer RJ, Buerk DG, Thom SR, Velazquez OC, unpublished observations). SPCs have been shown to home to ischemic wounds, where they are required for angiogenesis (3).

HBO_2 therapy is administered for a variety of maladies in a hyperbaric chamber where patients breathe pure O_2 at partial pressures up to 3.0 atmospheres absolute (ATA). HBO_2 is used in a standard fashion as prophylactic treatment to reduce the incidence of osteoradionecrosis (ORN) in patients who must undergo surgery involving tissues previously exposed to radiotherapy (6, 15). We obtained peripheral blood samples from

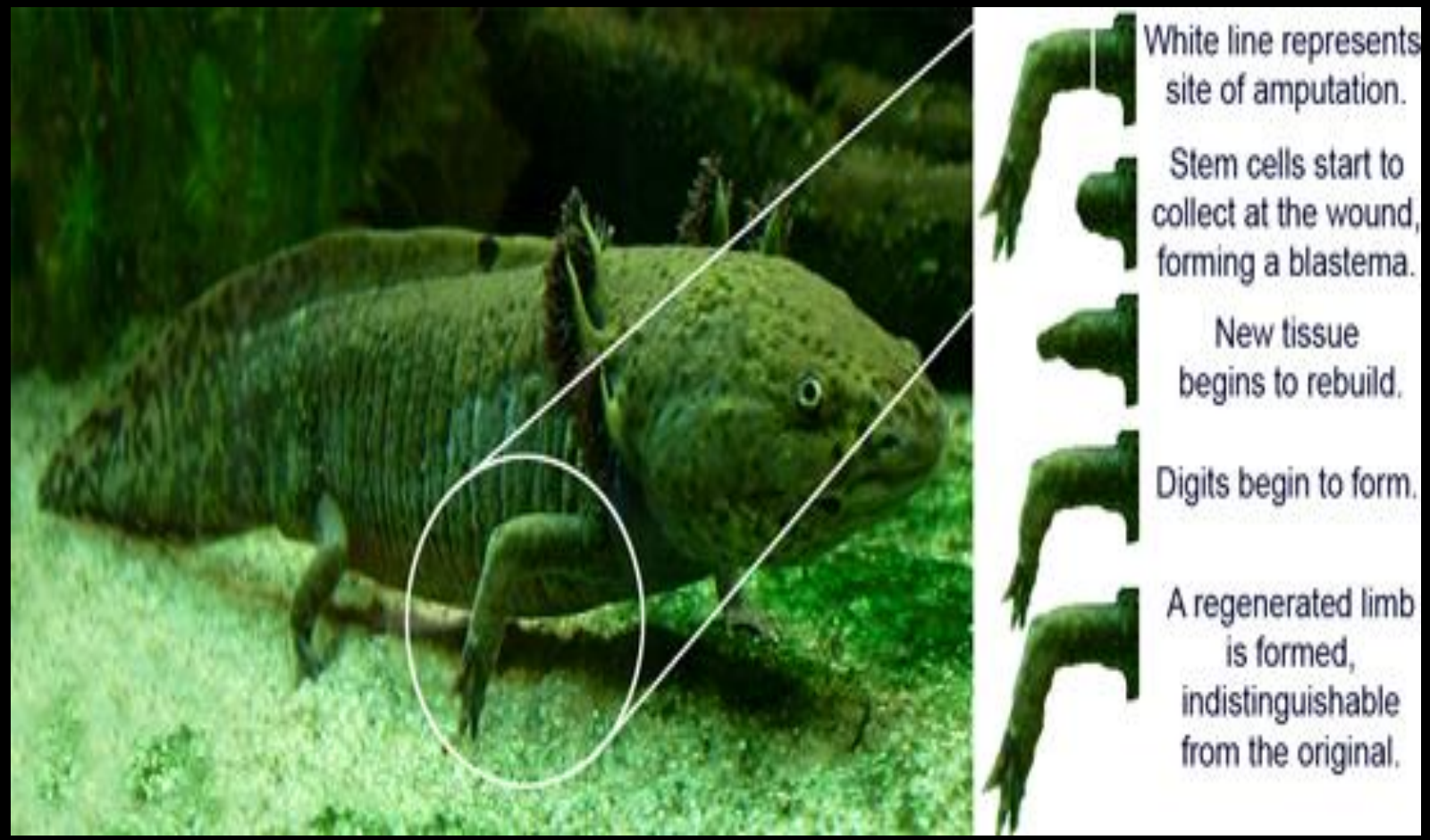
LESS STEM CELLS NEEDED THAN FORESEEN

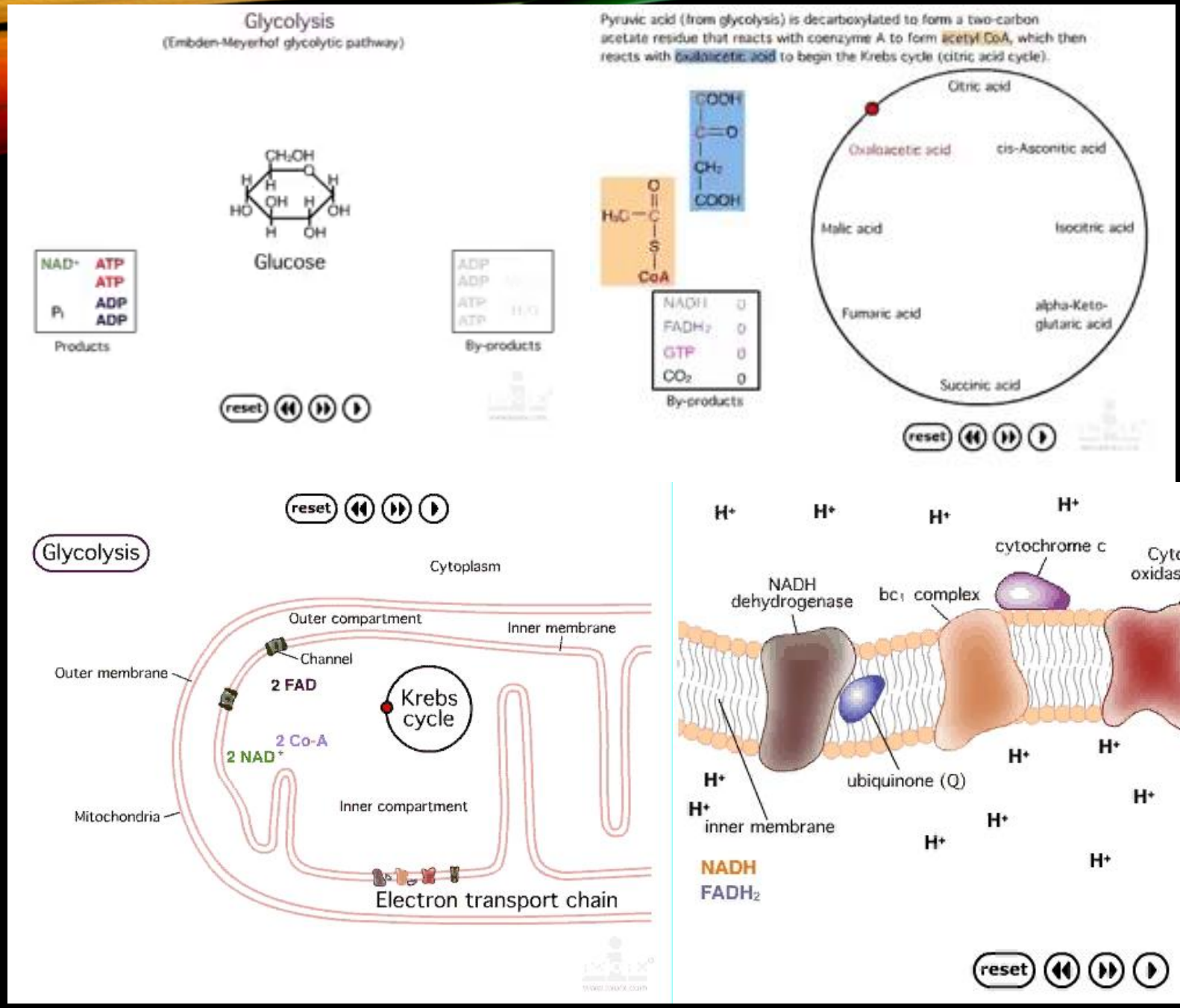
Shortly after the limb is amputated, the epithelium layer covers the exposed limb bud, forming the wound epithelium (WE).

A group of stem cells collects below this layer, forming the blastema.

The WE signals the stem cells below it to rebuild the limb, recreating the limb from the point of injury out towards the hand.

The final regenerated limb is indistinguishable from the original.




Glycolysis
(Embden-Meyerhof glycolytic pathway)
Glucose
NAD+ ATP
ATP
Pi ADP
ADP
Products
By-products
reset
Pyruvic acid (from glycolysis) is decarboxylated to form a two-carbon acetate residue that reacts with coenzyme A to form acetyl CoA, which then reacts with oxaloacetic acid to begin the Krebs cycle (citric acid cycle).
CoA
NADH 0
FADH2 0
GTP 0
CO2 0
By-products
Citric acid
cis-Aconitic acid
Isocitric acid
alpha-Keto-glutaric acid
Succinic acid
Fumaric acid
Malic acid
Oxaloacetic acid
reset
reset
Glycolysis
Cytoplasm
Outer compartment
Inner membrane
Channel
Outer membrane
2 FAD
Krebs cycle
2 Co-A
2 NAD+
Inner compartment
Mitochondria
Electron transport chain
Outer compartment of mitochondrion
cytochrome c
Cytochrome oxidase complex
Channel protein
O oxygen
NADH dehydrogenase
bc1 complex
ubiquinone (Q)
inner membrane
Inner compartment of mitochondrion
NADH
FADH2
Pi
ADP
reset

WHAT DOSE DO WE NEED…….ARE WE USING TOO HIGH DOSES?

FISH AND MOUSE

THERAPEUTIC USE OF ENVIRONMENTAL CHANGES

- Apart from some « sanatoria » and other plane fligths to cure pertussis.
- The real therapeutic use of environmental changes combined Oxygen and Pressure

ORIGINAL PAPERS

Life without blood

tudy of the influence of high atmospheric pressure and hypothern
on dilution of the blood)

by

I. BOEREMA (*), N. G. MEYNE, W. K. BRUMMELKAMP
BOUMA, M. H. MENSCH, F. KAMERMANS, M. STERN HANF
and W. VAN AALDEREN
rom the Surgical Department of the University of Amsterdam)

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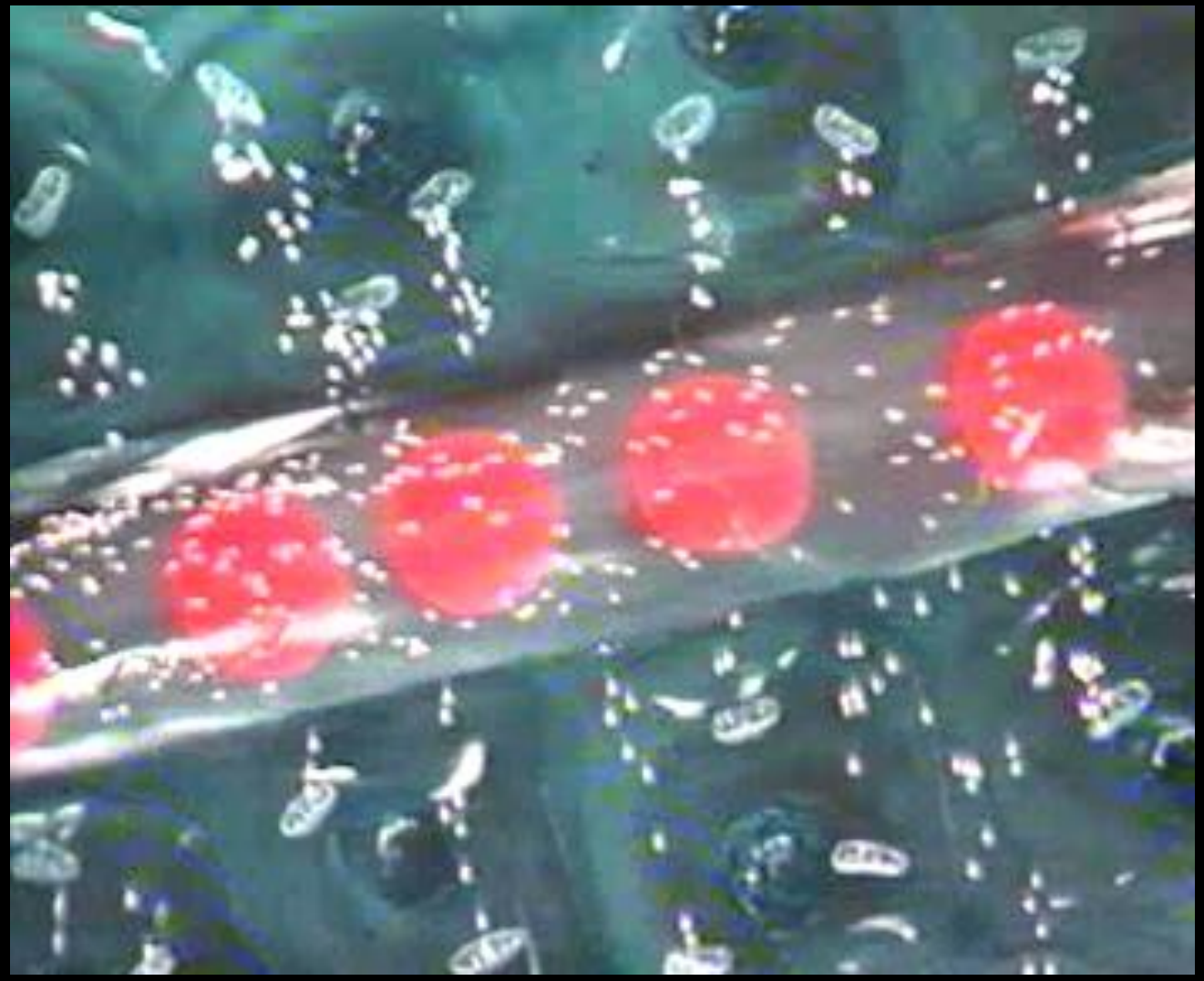
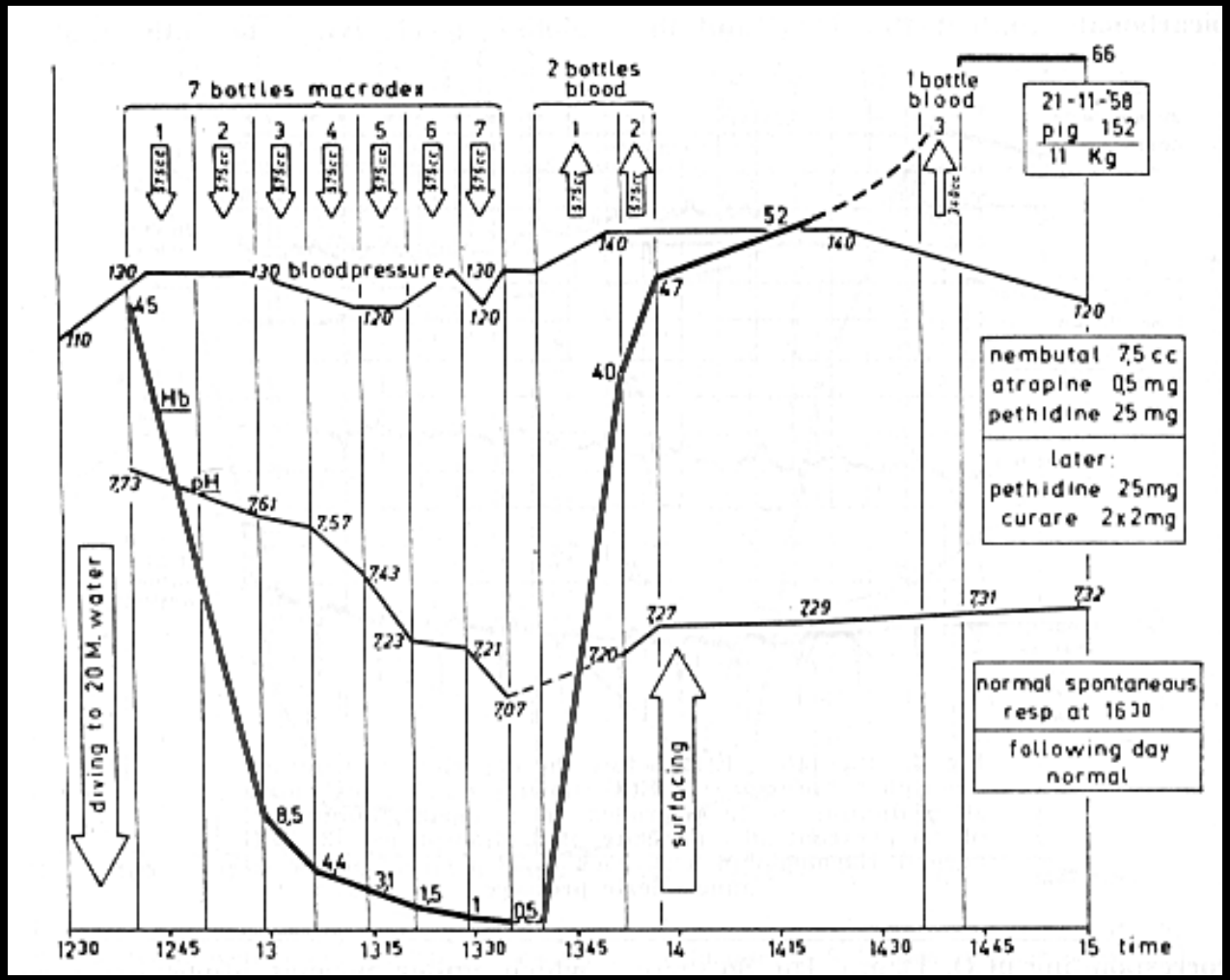
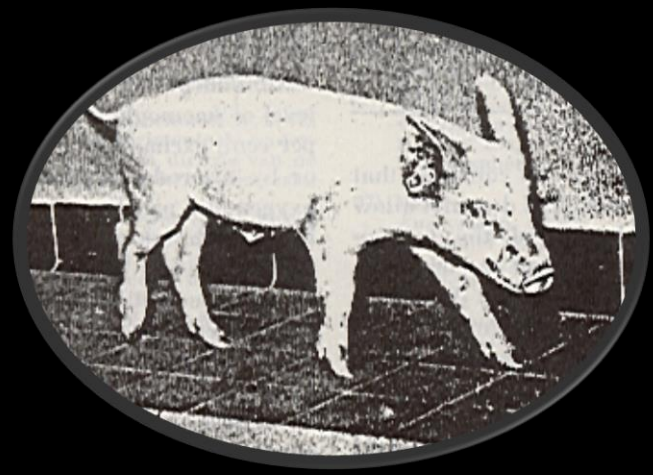


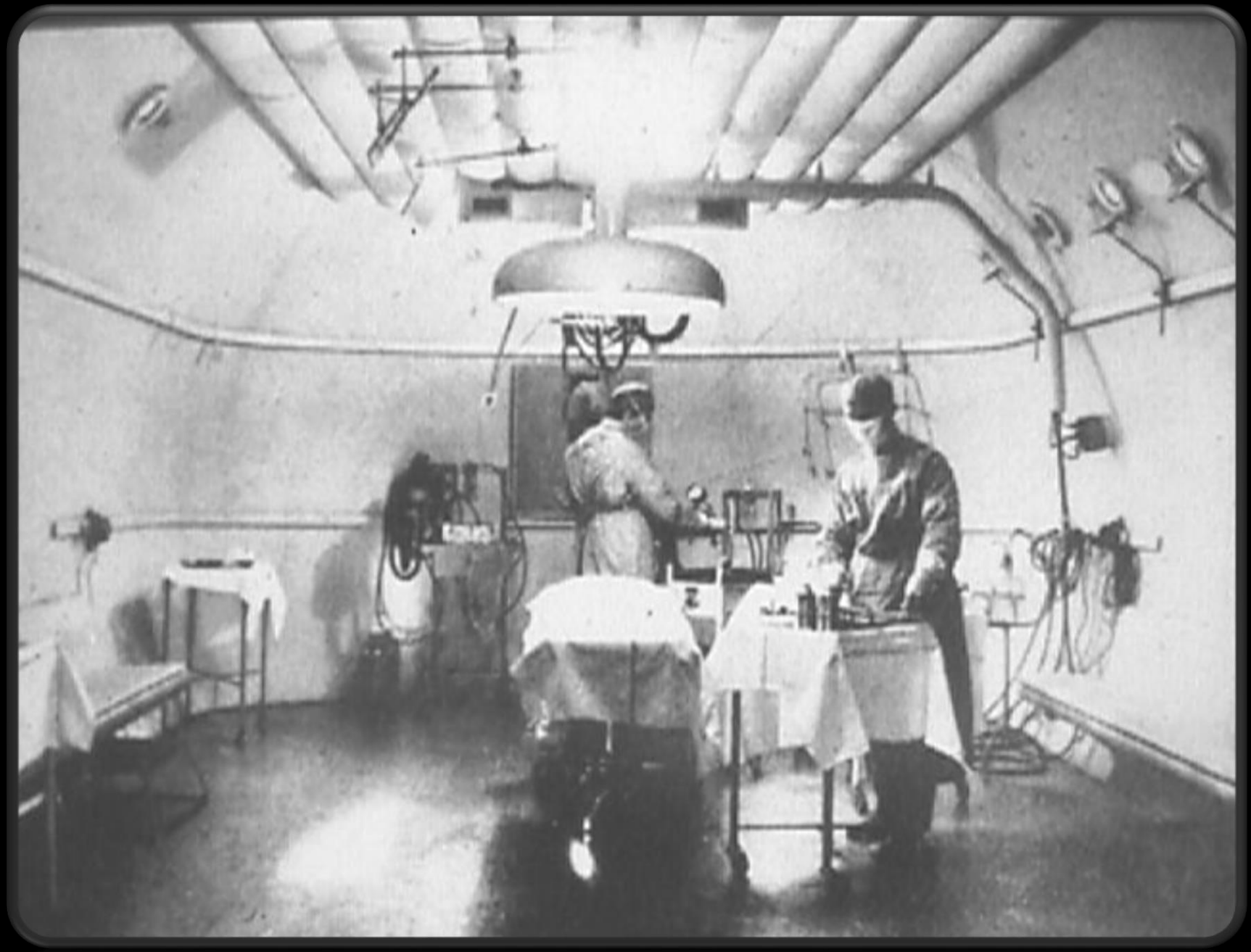
LIFE WITHOUT BLOOD
BOEREMA 1960

« LIFE WITHOUT BLOOD »
BOEREMA 1960





Hyperbaric oxygen.
20 m depth.
0,5 % hématocrit



EMPIRICAL USE, ADAPTATION OF WHAT WAS ALREADY USED FOR DIVERS

Is empirism wrong?

WOULD A TOO LOW DOSE BE A PLACEBO?

THE PERFECT PROTOCOL

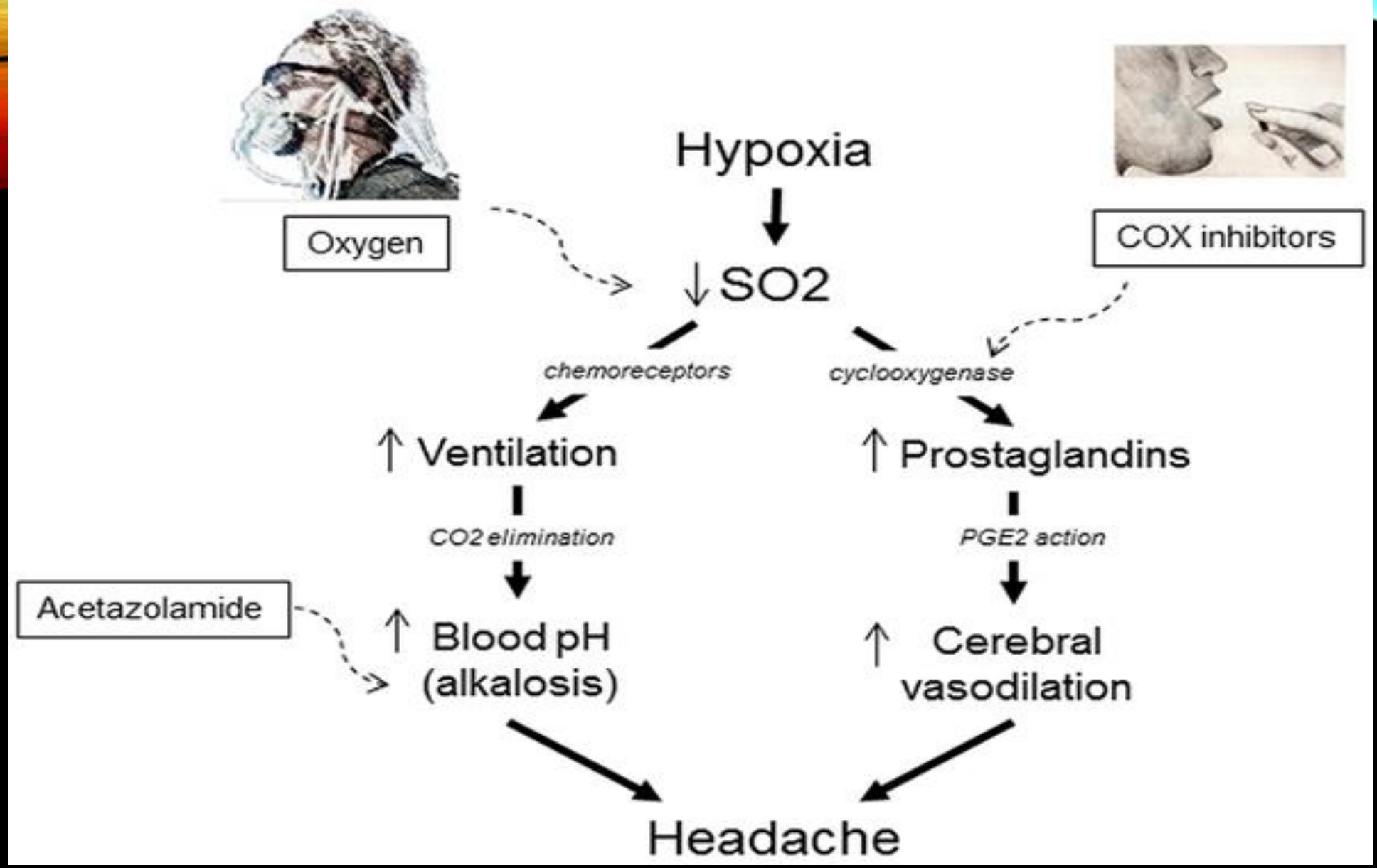
- One homogenous sample measured before and after intervention

- The same sample being mesured before and after the time needed for the intervention but without it

- Time machine needed !!

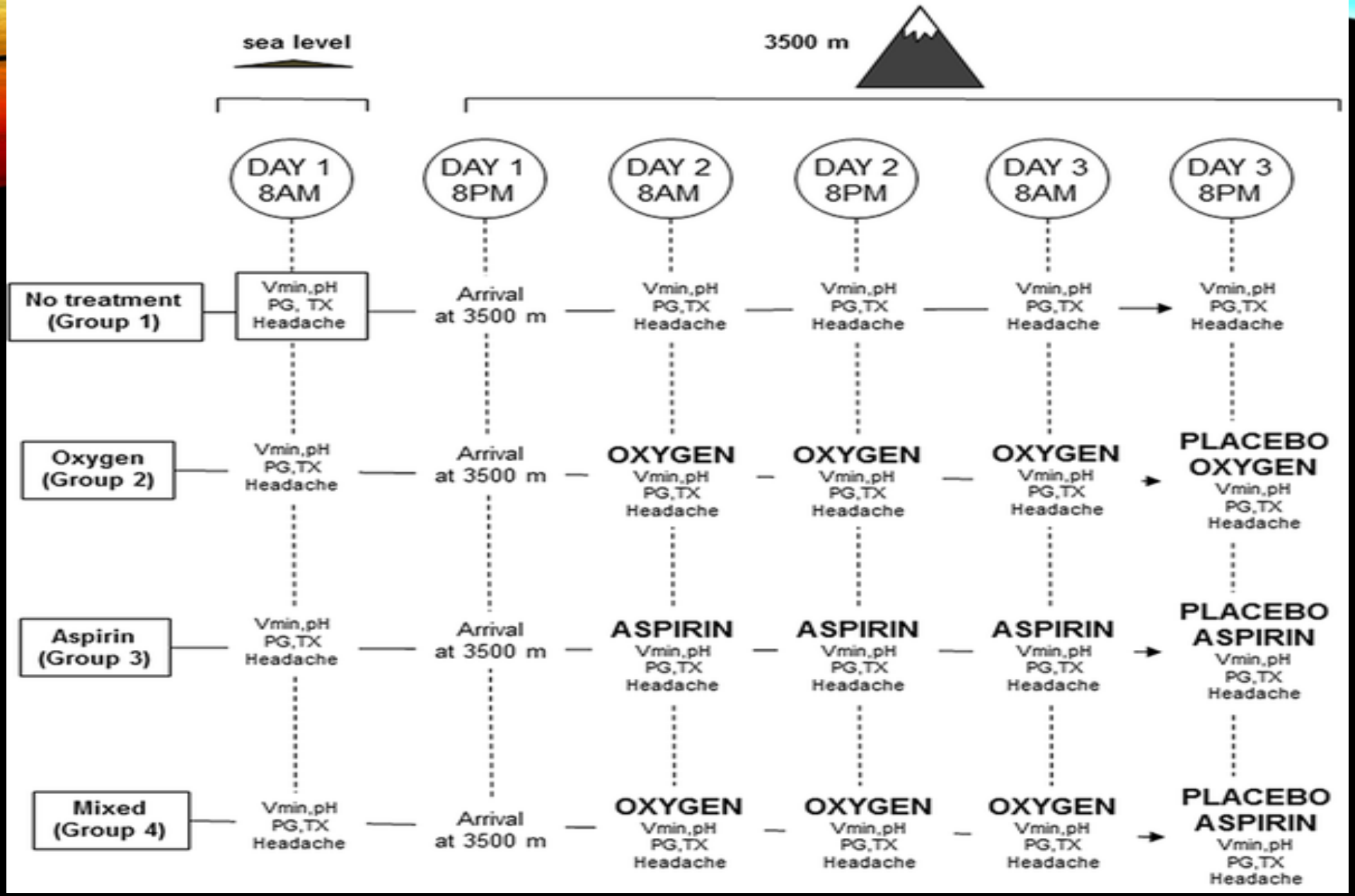
PLACEBO

The term “placebo” comes from the St. Jerome’s Latin translation of the Bible in Psalm 114:9 *Placebo Domino in regione vivorum*: “I will please”. This reference was used in the offices for the dead and is related to liturgy that funnels by definition a number of feelings, sensibility, understanding and analysis.



Benedetti F, Dogue S (2015) Different Placebos, Different Mechanisms, Different Outcomes: Lessons for Clinical Trials. PLoS ONE 10(11): e0140967. doi:10.1371/journal.pone.0140967
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967

Fig 1. Rationale of the study.



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http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967

Fig 2. Experimental design.

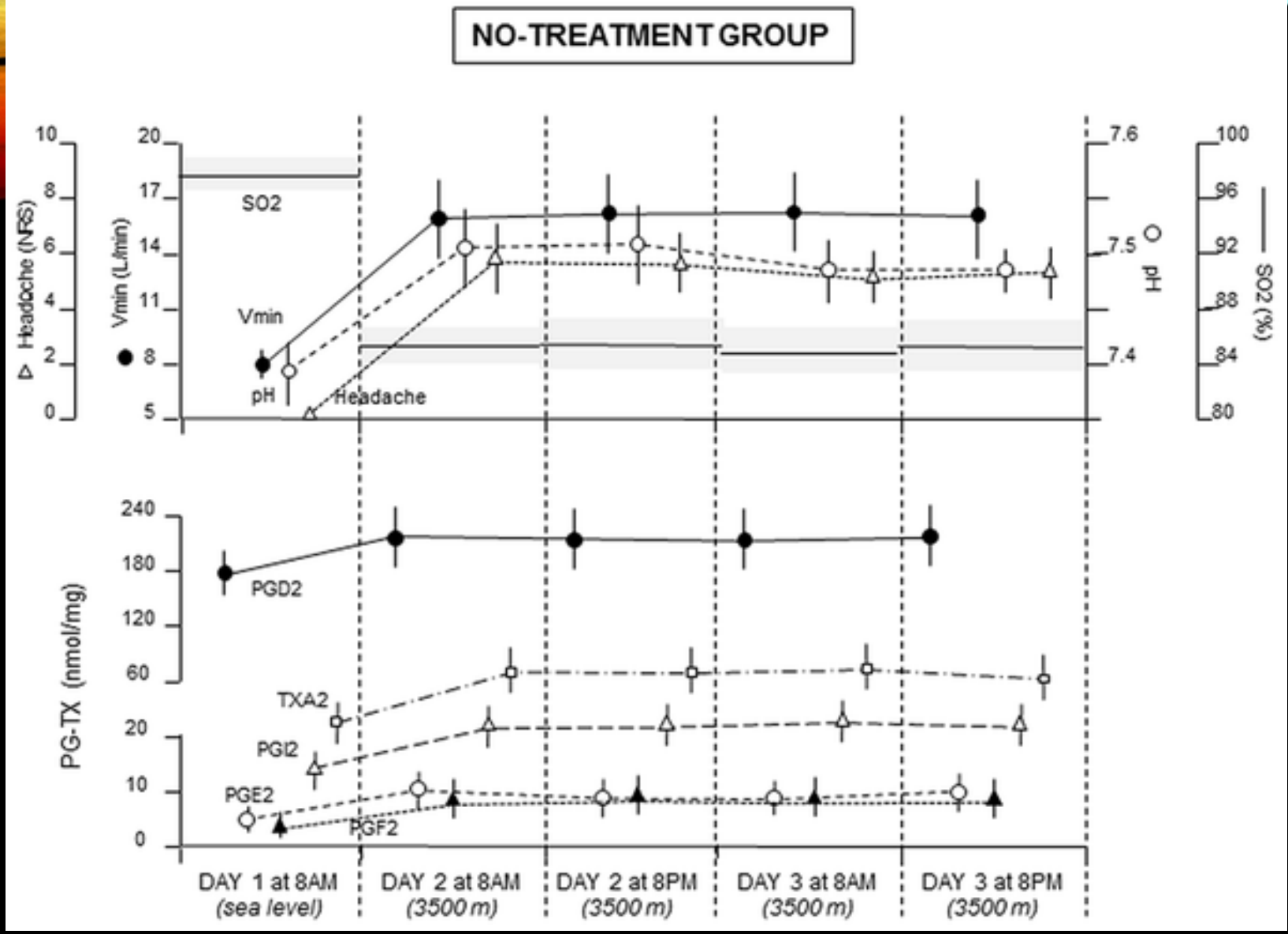

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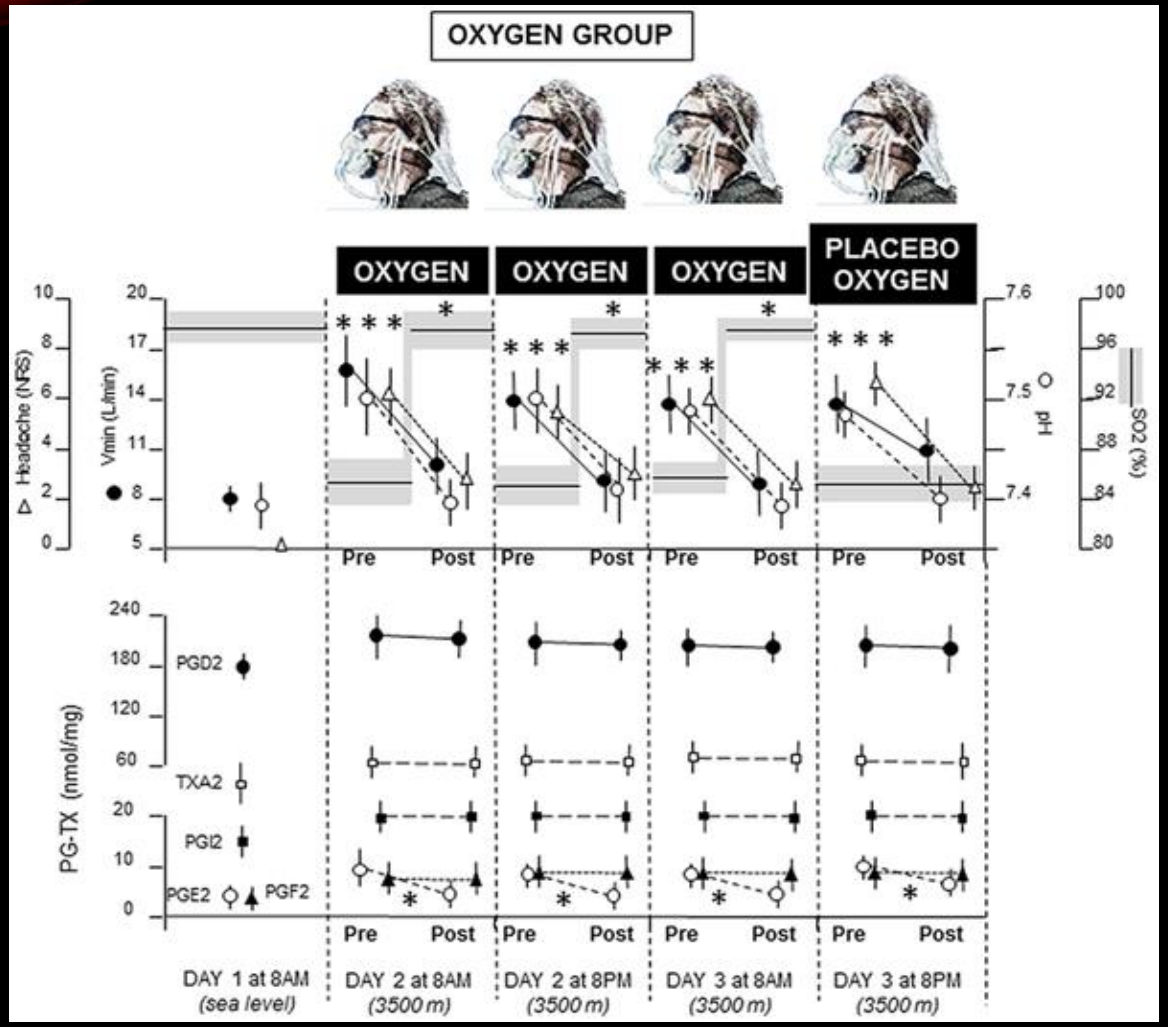
Fig 3. No-treatment group.

Fig 4. Means (+SD) for all the measurements in the oxygen group.



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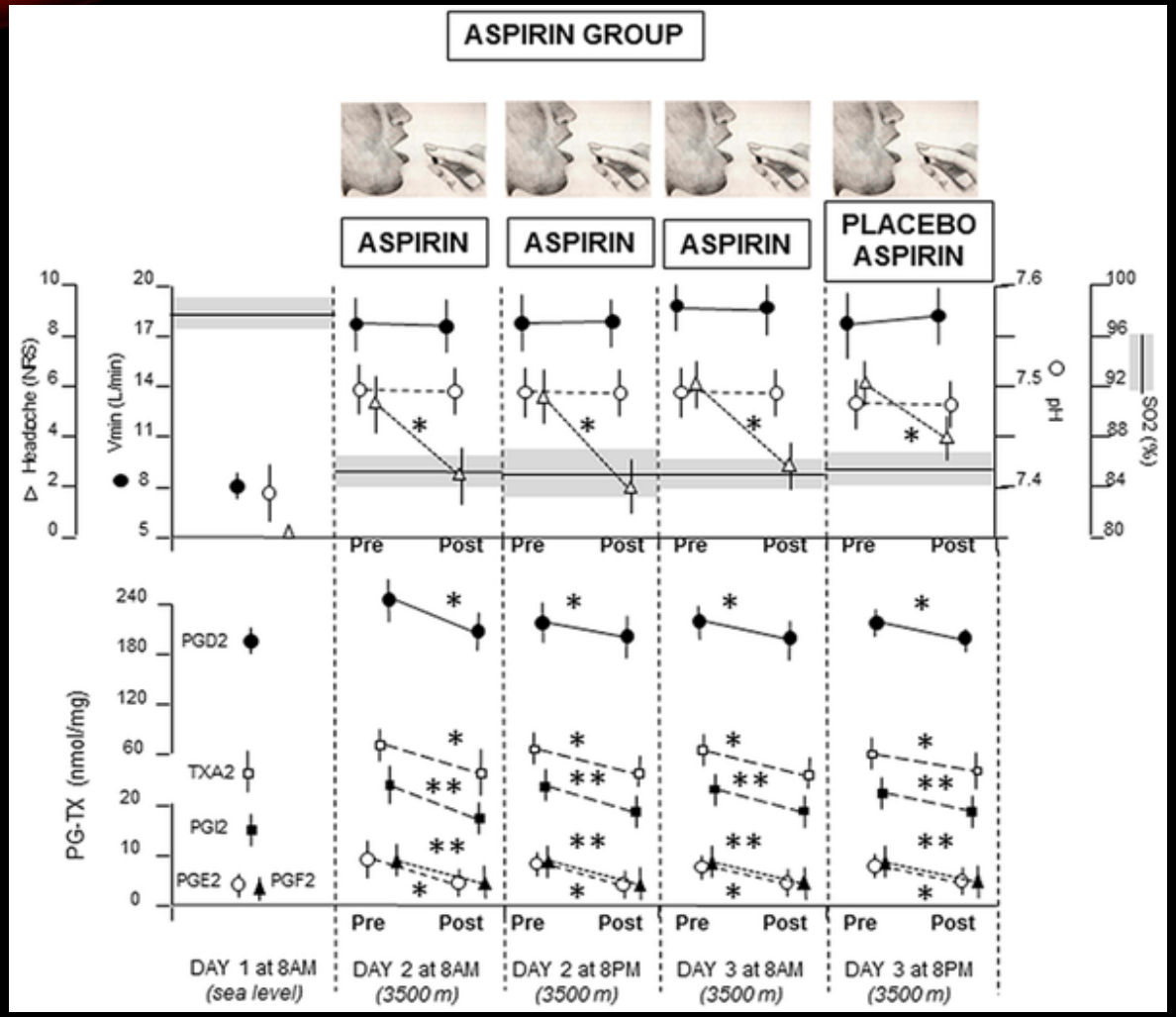
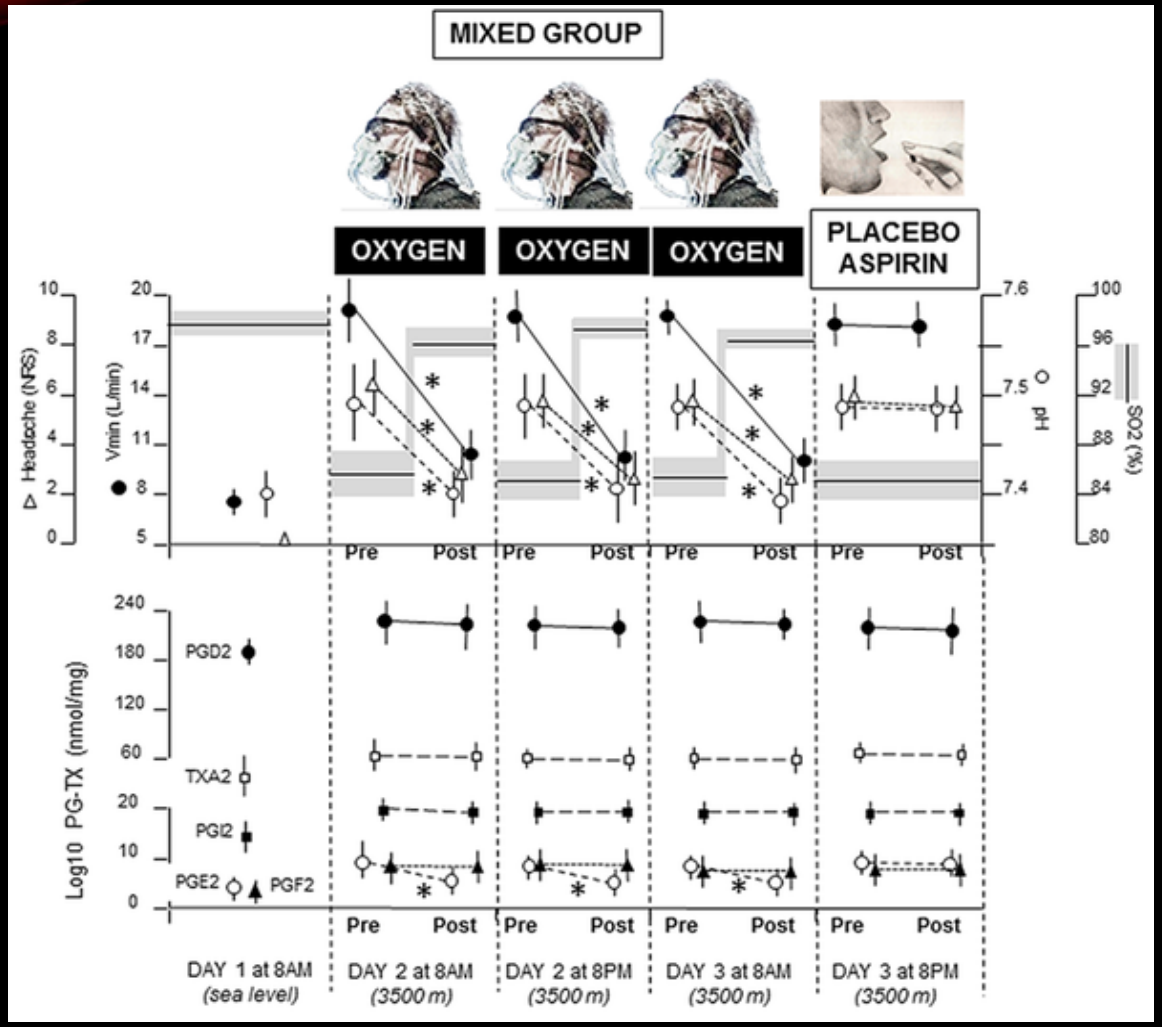
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967

Fig 5. Means (+SD) for all the measurements in the aspirin group.



Benedetti F, Dogue S (2015) Different Placebos, Different Mechanisms, Different Outcomes: Lessons for Clinical Trials. PLoS ONE 10(11): e0140967. doi:10.1371/journal.pone.0140967
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967

Fig 6. Means (+SD) for all the measurements in the mixed group.



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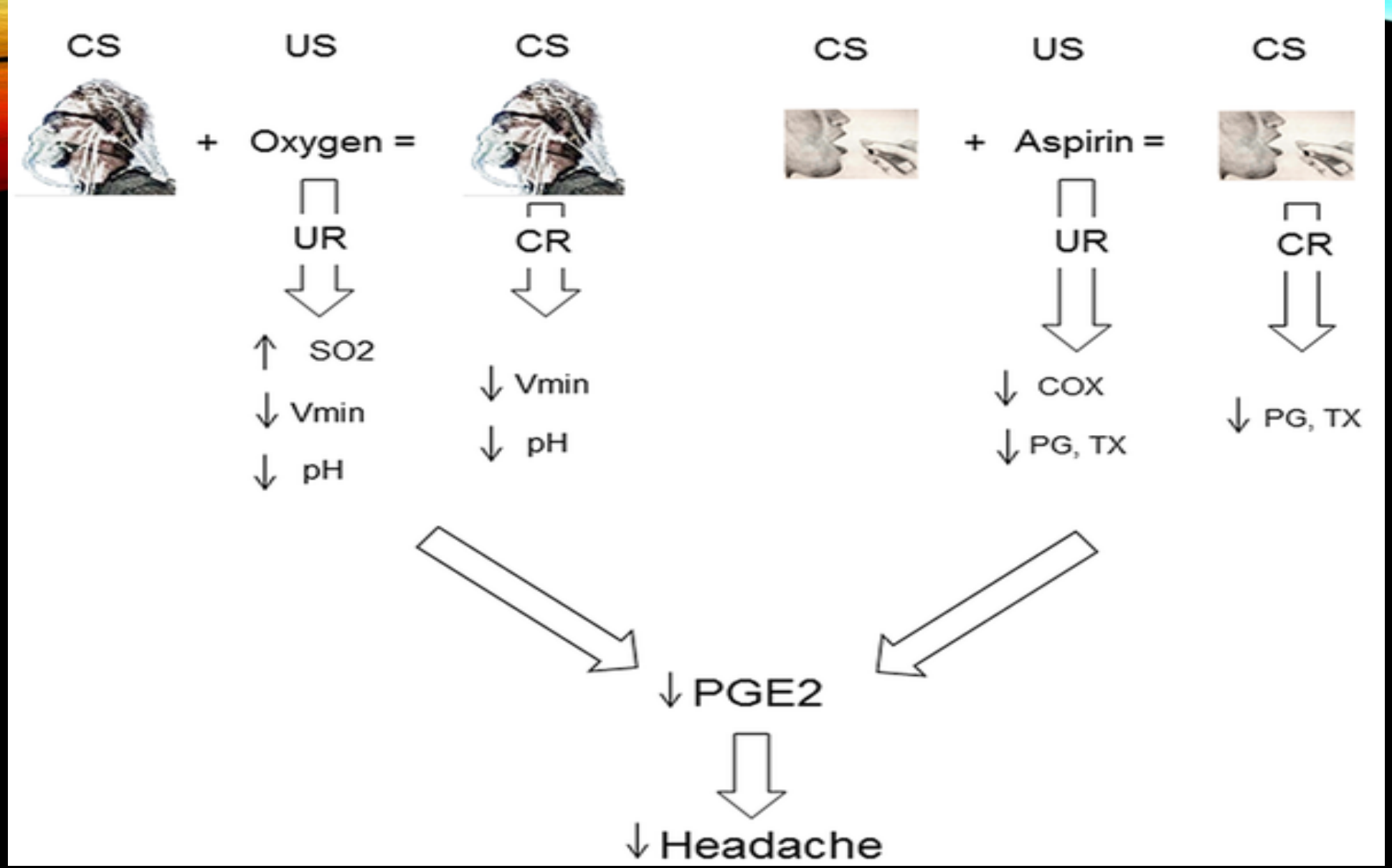

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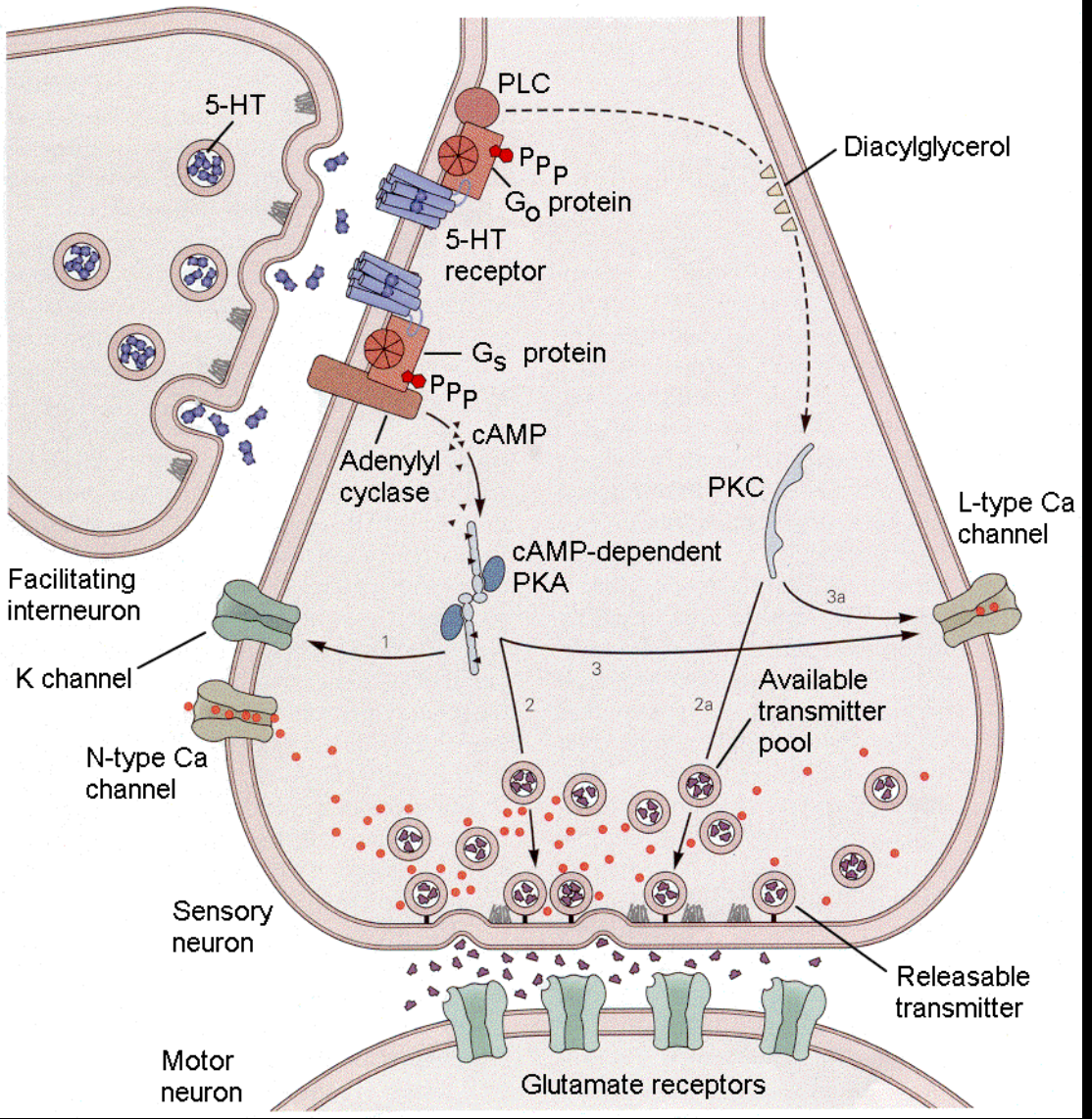
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0140967

Fig 8. Model that explains the findings of the present study.

PLOS ONE



Eric Kandel – Aplysia Californica

IN A NUTSHELL

- Ritual is the clue, mixing placebos doesn't work (goes back to the origin of placebo)
- Physiotherapy sessions or Hyperbaric Oxygen sessions are a «ritual» by essence.
- It appears that totally exclude placebo effect is not feasible.

MISTAKE…….

IF VASCULARISATION IS STILL PRESENT AND EFFECTIVE
LOWER DOSES ARE OF INTEREST

NORMOBARIC OXYGEN & LYMPH DRAINAGE

Original Research

Normobaric oxygen can enhance protein captation by the lymphatic system in healthy humans.

C. BALESTRA[1,2,3*] P. GERMONPRÉ[1,4*], T. SNOECK[1,2,3], M. EZQUER[1,2,3], O. LEDUC[2], A. LEDUC[2], F.WILLEPUT[2], A. MARRONI[1], R. CALI CORLEO[1], R. VANN[1]

[1]DAN Europe, IDAN Research Division. [2]Université Libre de Bruxelles Institut Supérieur d'Education Physique et Kinésithérapie, Brussels, Belgium. [3]Haute Ecole Paul Henri Spaak, General Human Biology Dept., Brussels, Belgium. [4]Center for Hyperbaric Oxygen Therapy, Military Hospital Queen Astrid, Brussels, Belgium.
** These authors contributed equally to the work.*

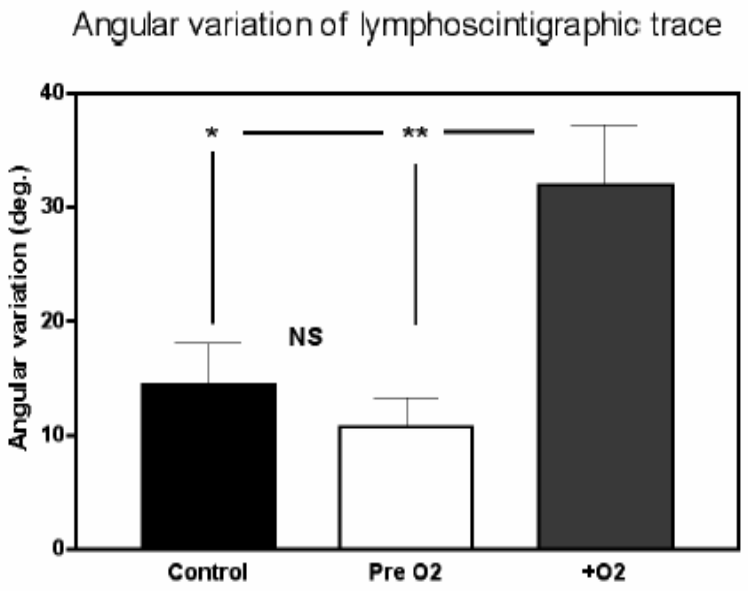
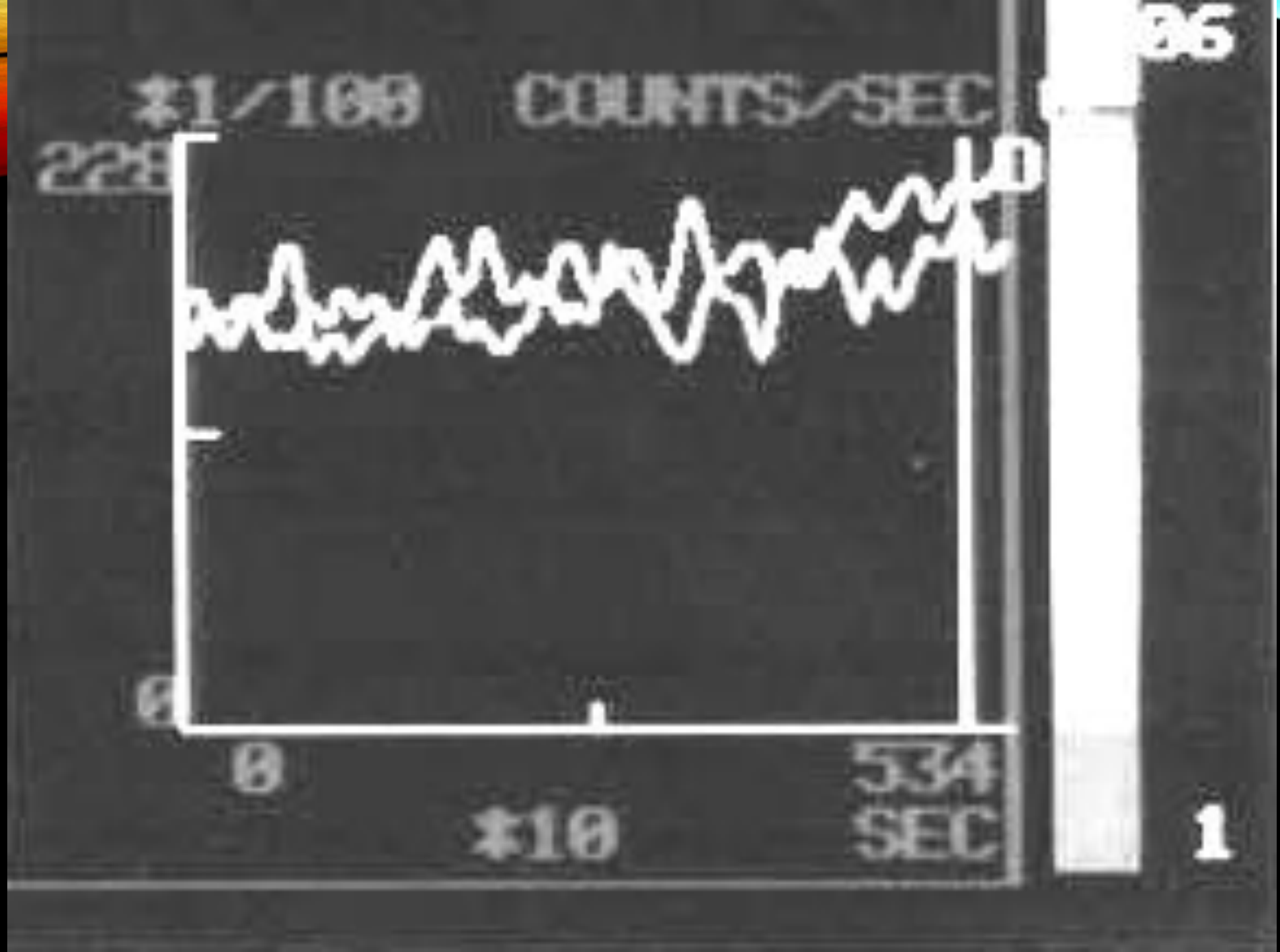
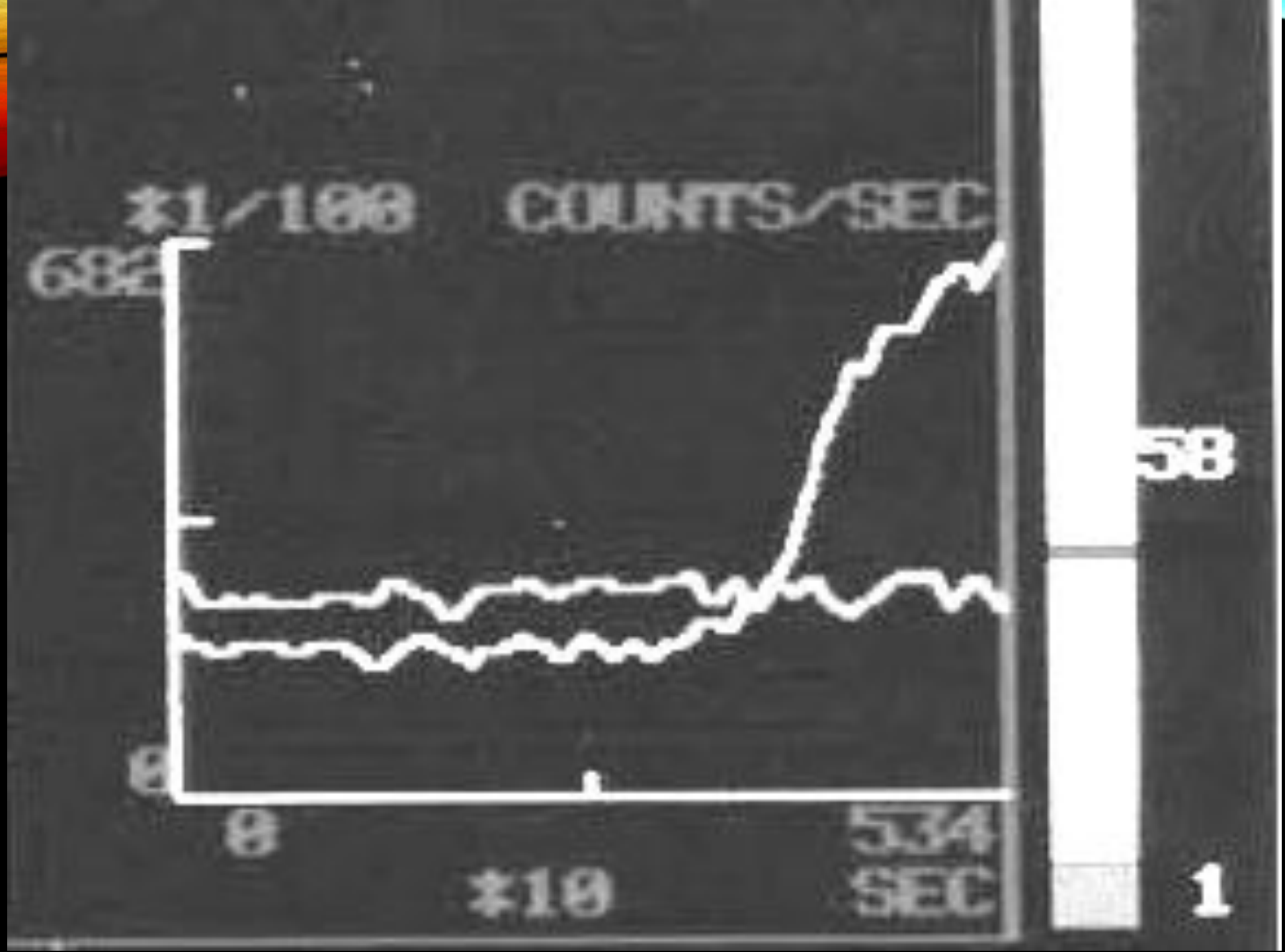


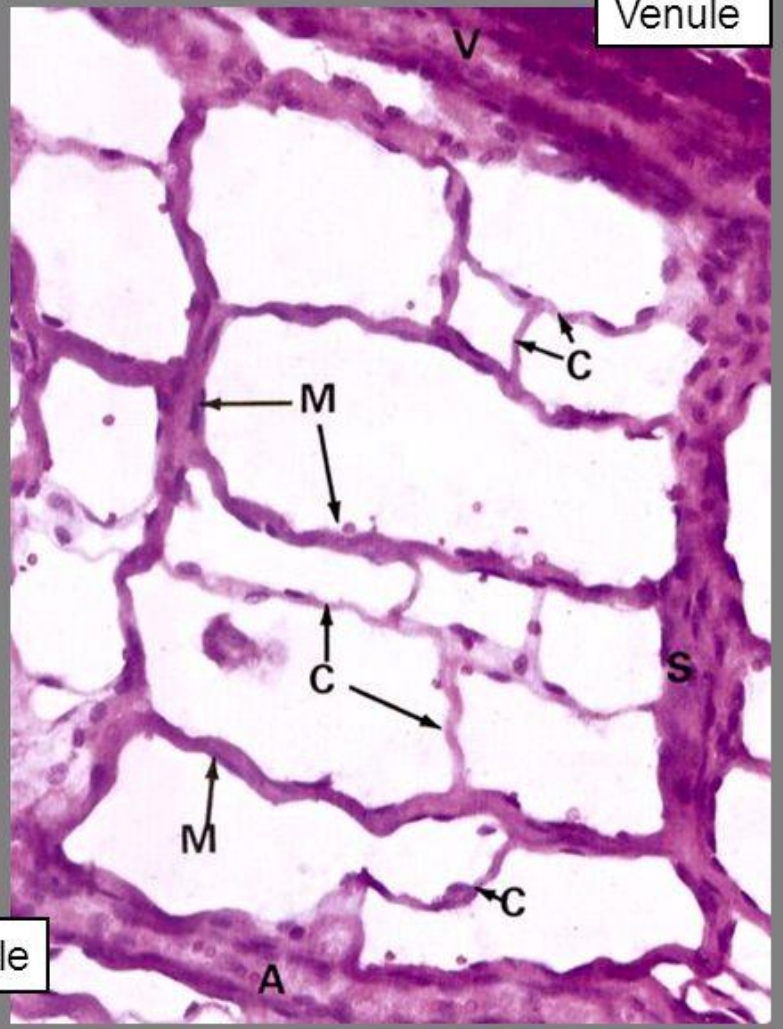
Figure 2. Statistical comparison between the control absorption speed (angular variation) in the axillary region; the pre-oxygen situation and after 30 minutes of normobaric oxygen breathing.*=p>0,05; **=p>0,01


*1/100 COUNTS/SEC
0
534
SEC
*10
1


*1/100 COUNTS/SEC
682
0
0
534
*10
SEC
58
1

Microvascular unit

Venule



Metarteriole

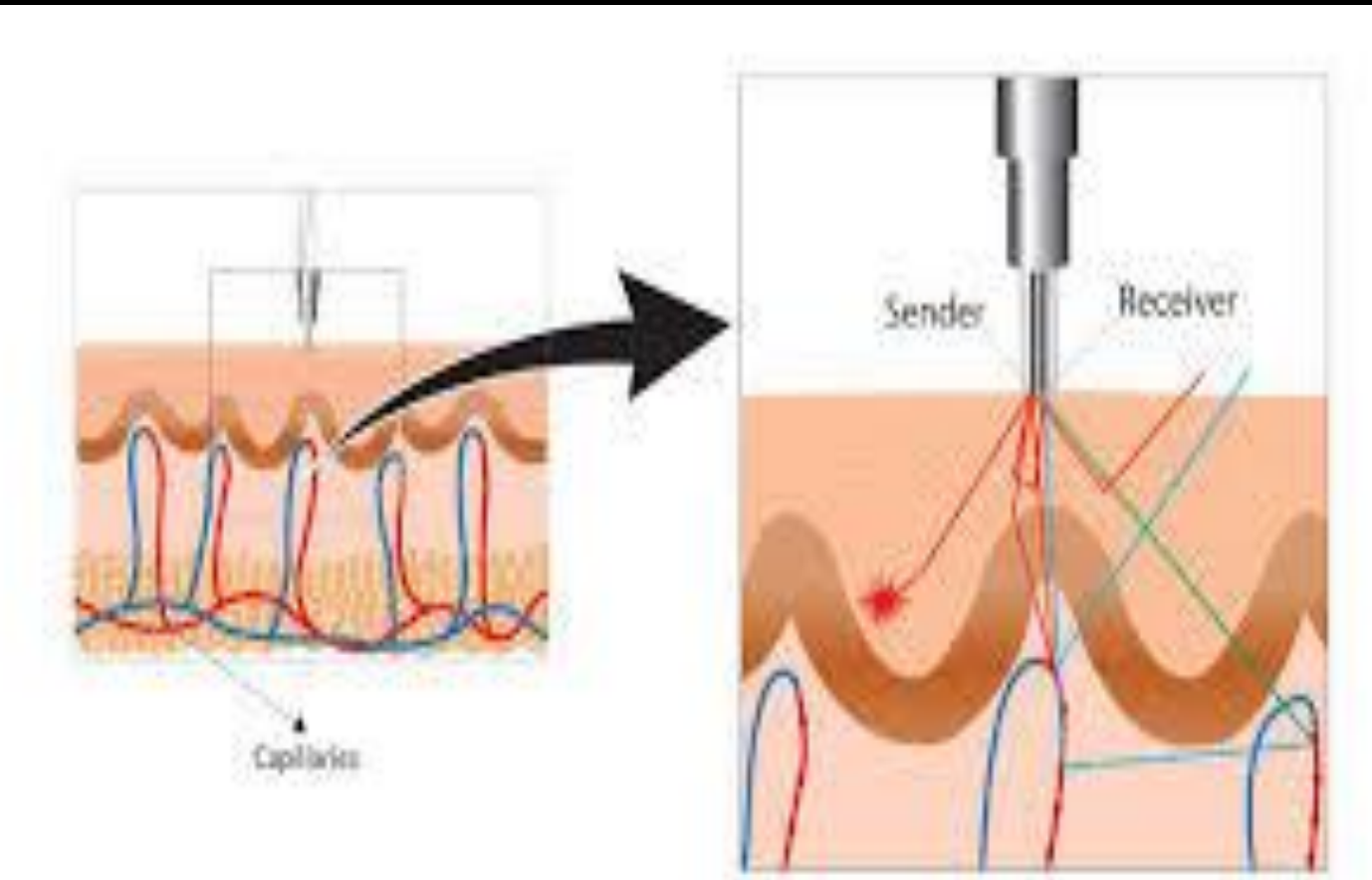
Capillaries

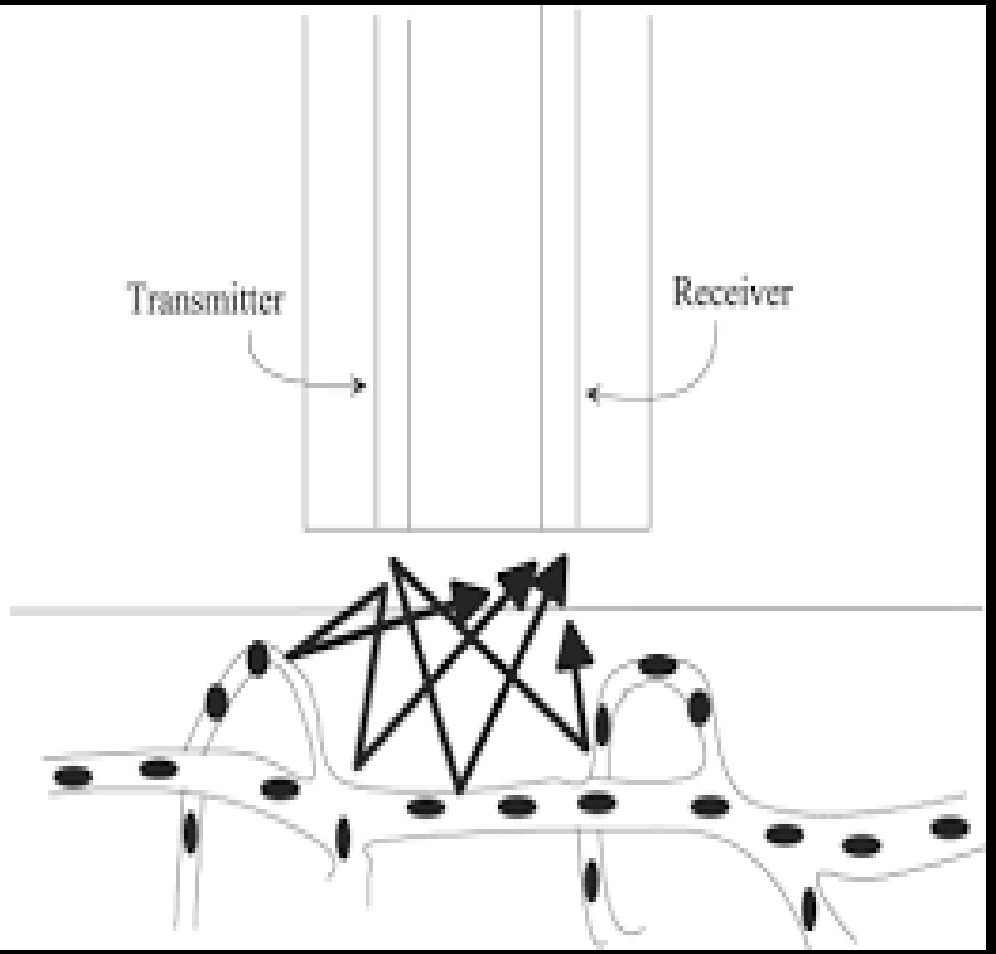
Arteriole

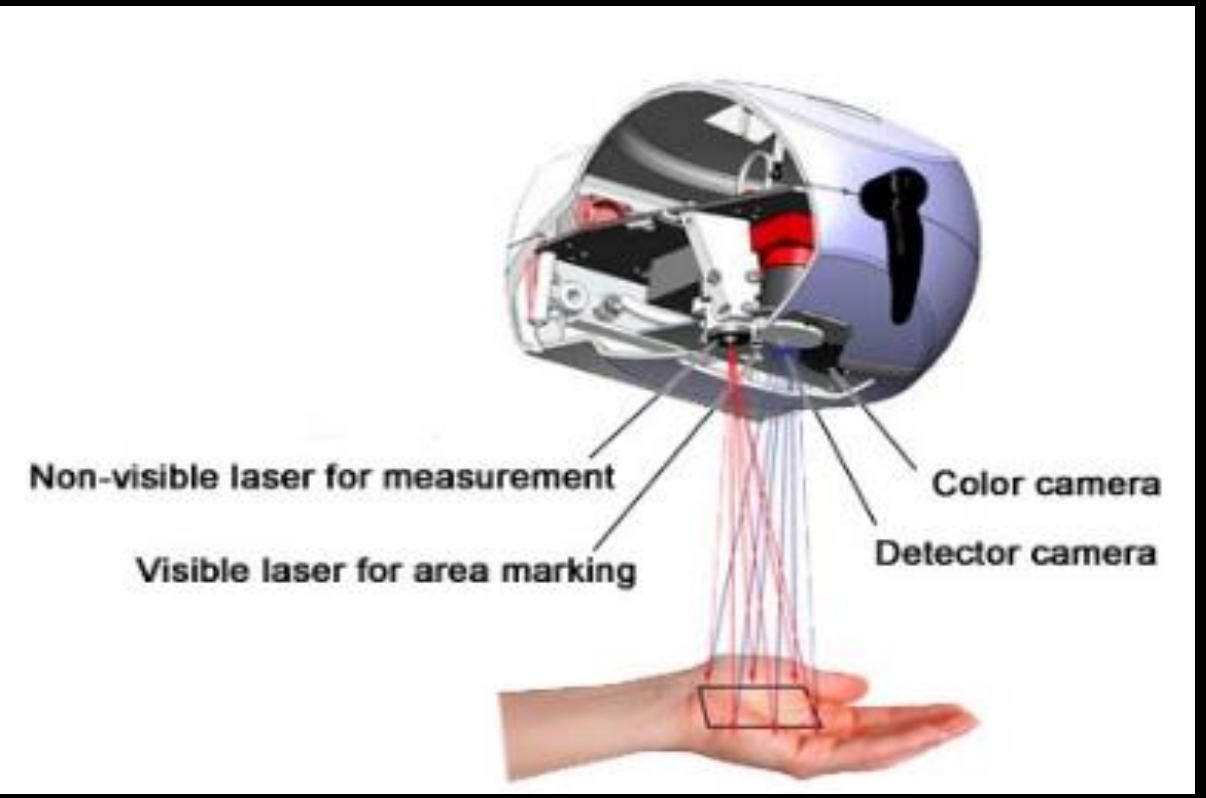
Arteriovenous shunt (S)

Pre-capillary sphincters exist at the origin of each capillary

LASERFLOW SPECKLE DOPLLER






Non-visible laser for measurement
Visible laser for area marking
Color camera
Detector camera

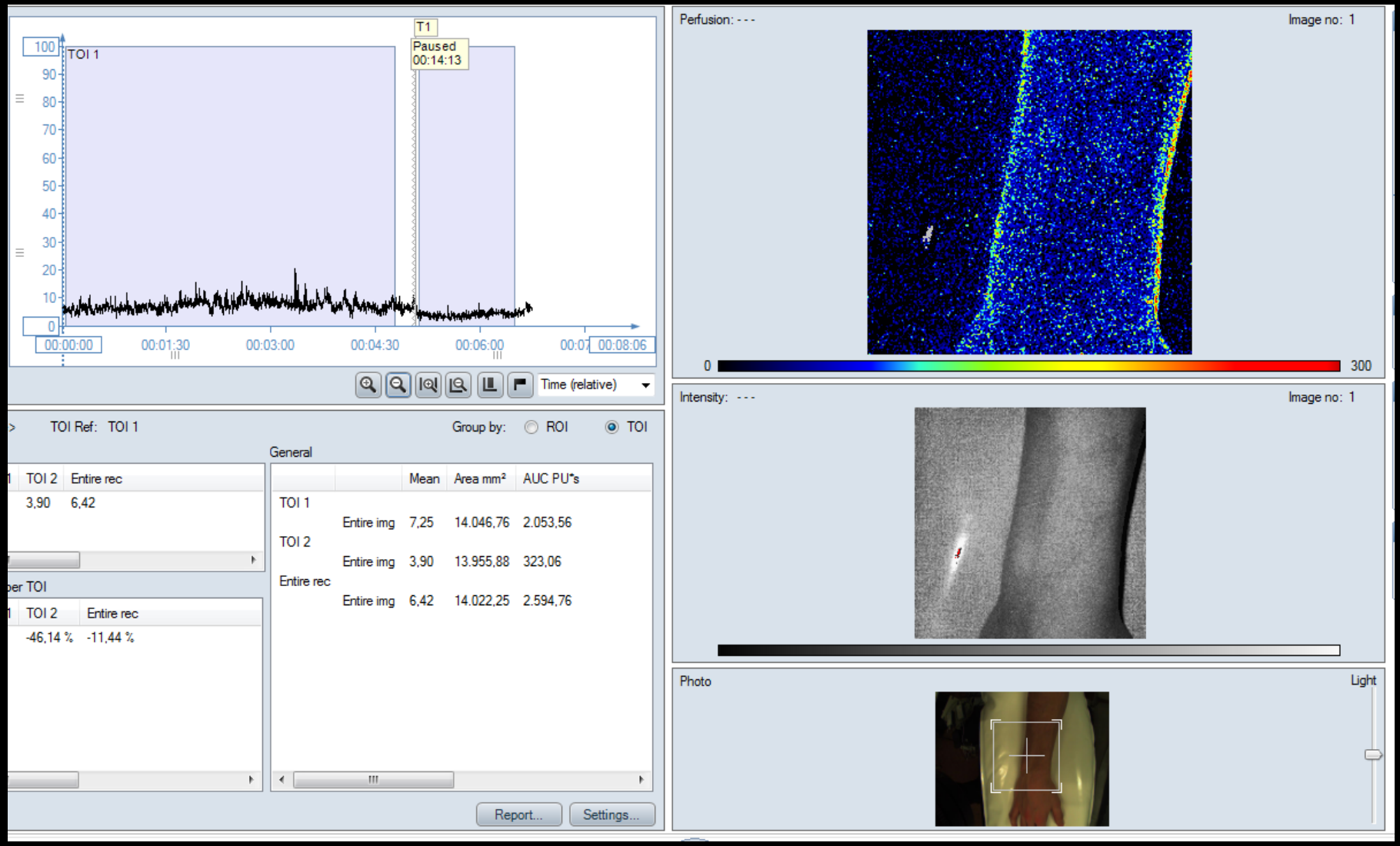

1


2

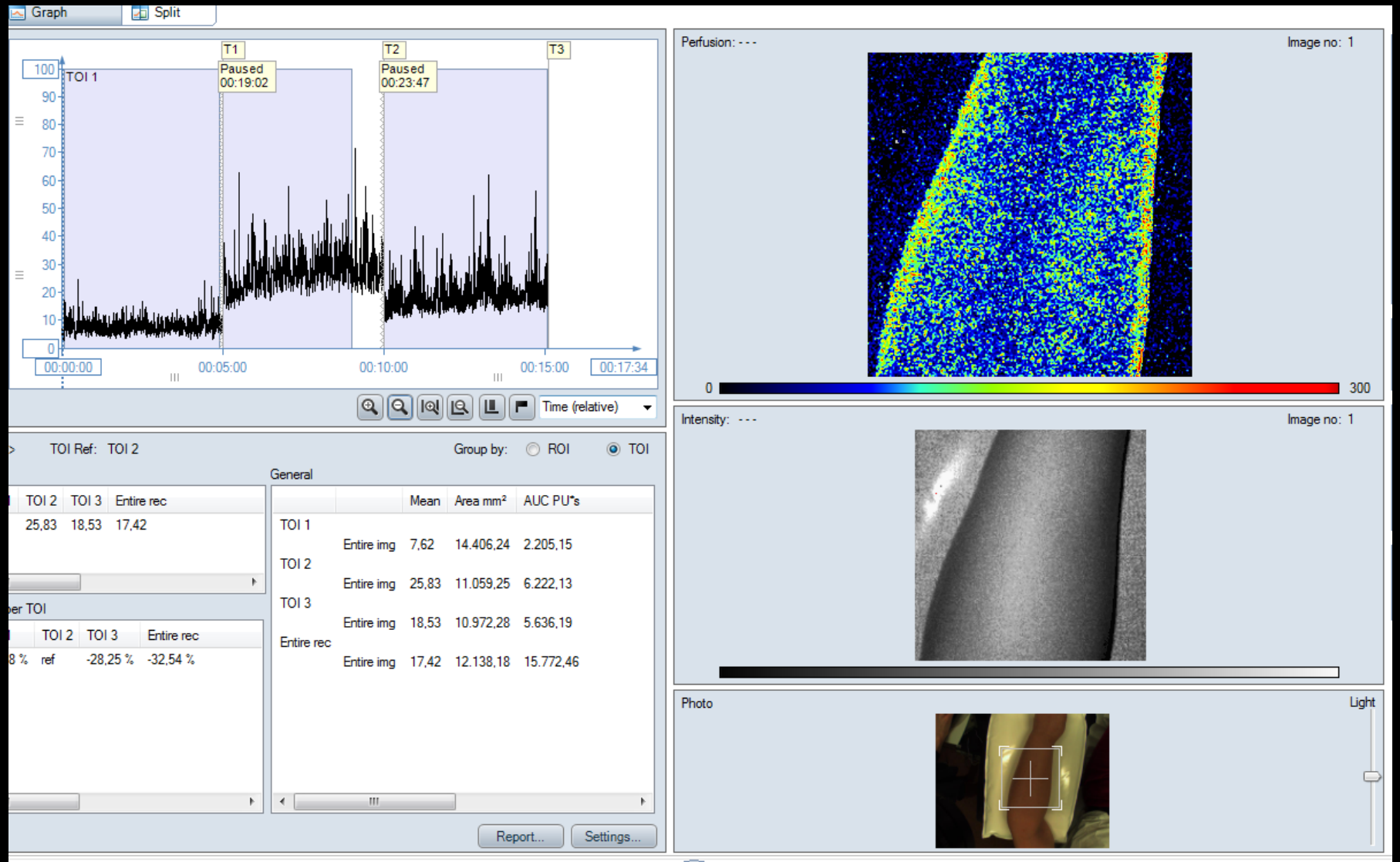

3

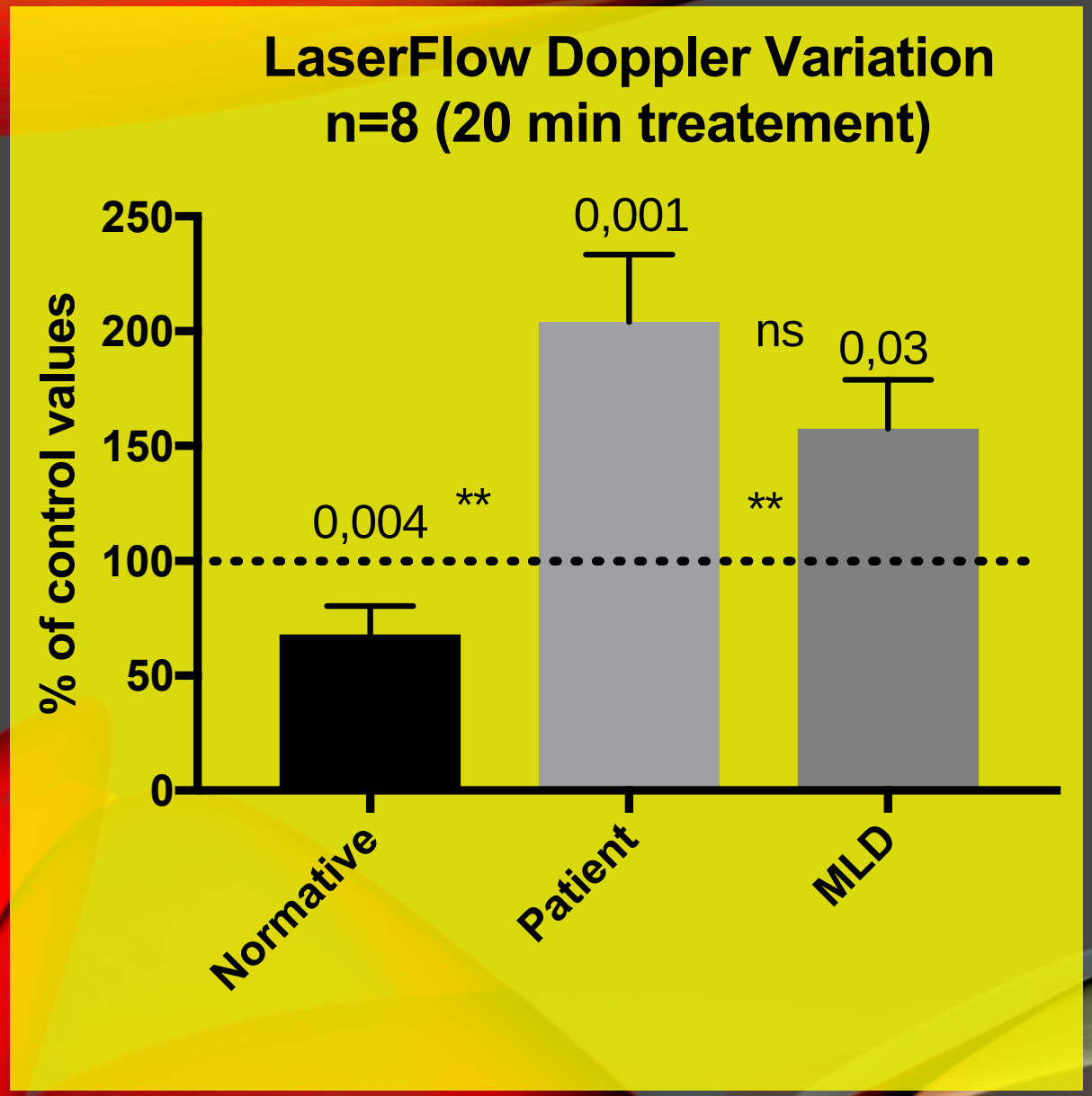
UPPER LIMD EDEMA TREATEMENT

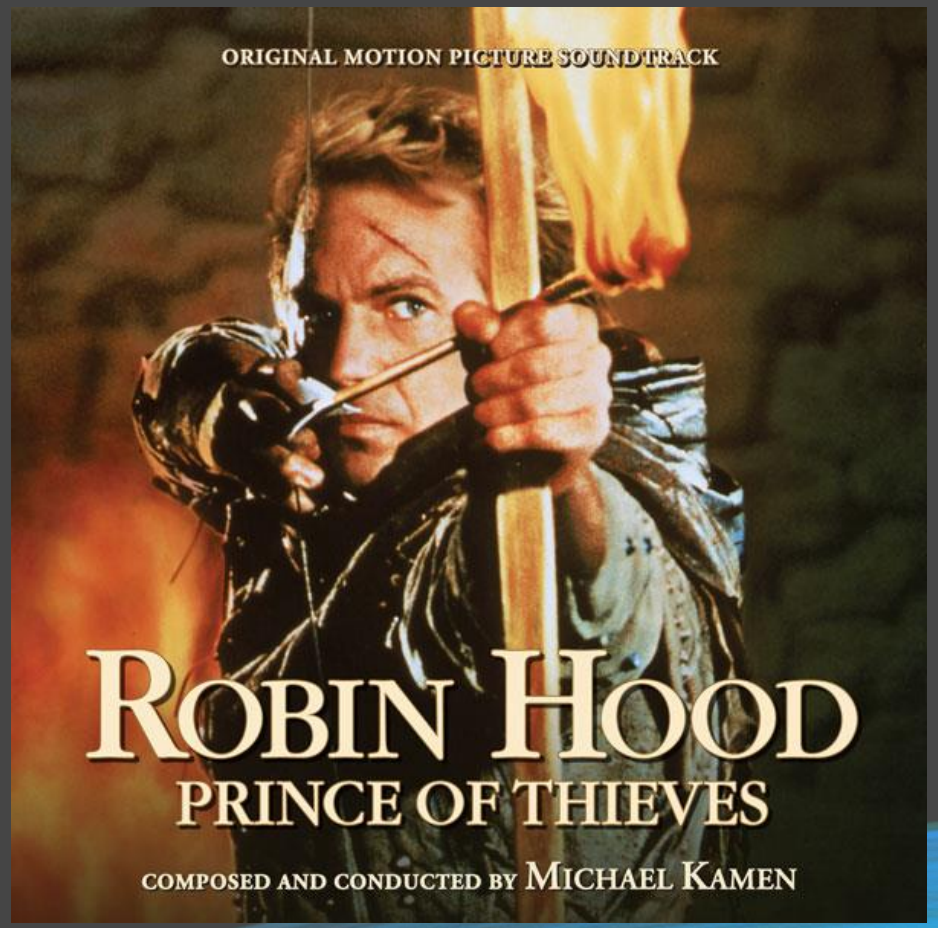
CUTANEOUS PERFUSION NO EDEMA (MICROVASCULARISATION)

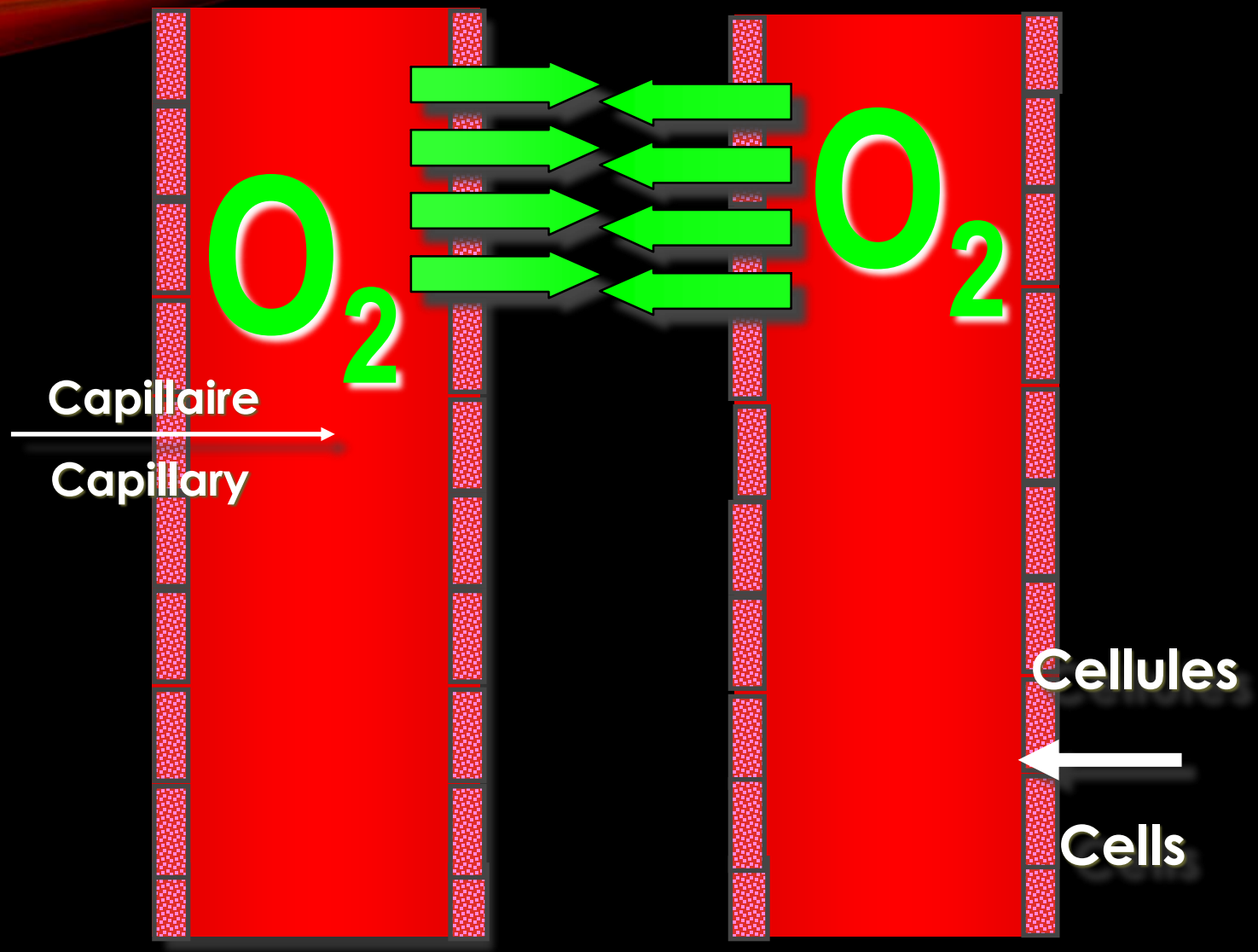


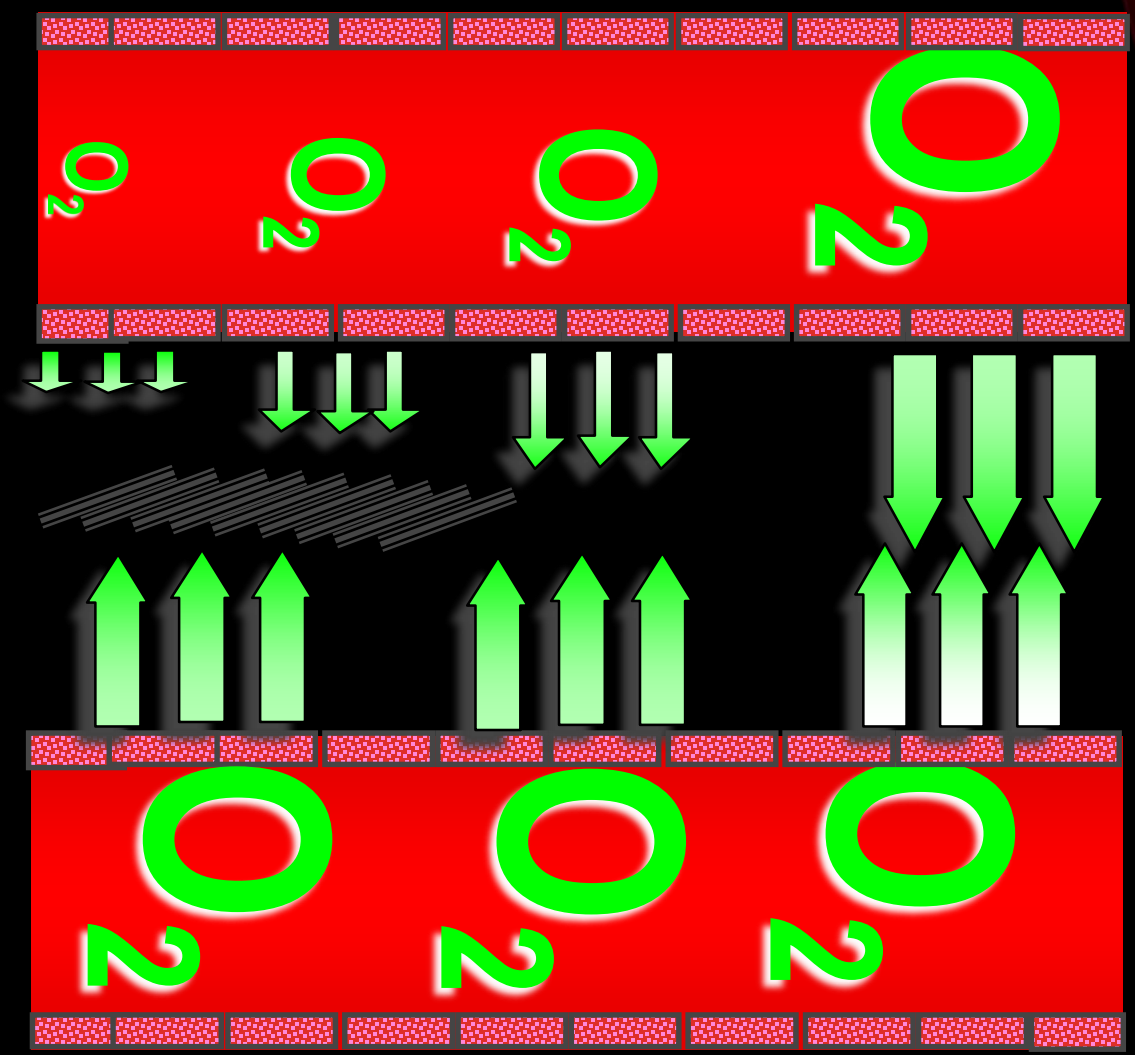
PERFUSION LYMPHOEDEMA (AXYLLARY LYMPHECTOMY)

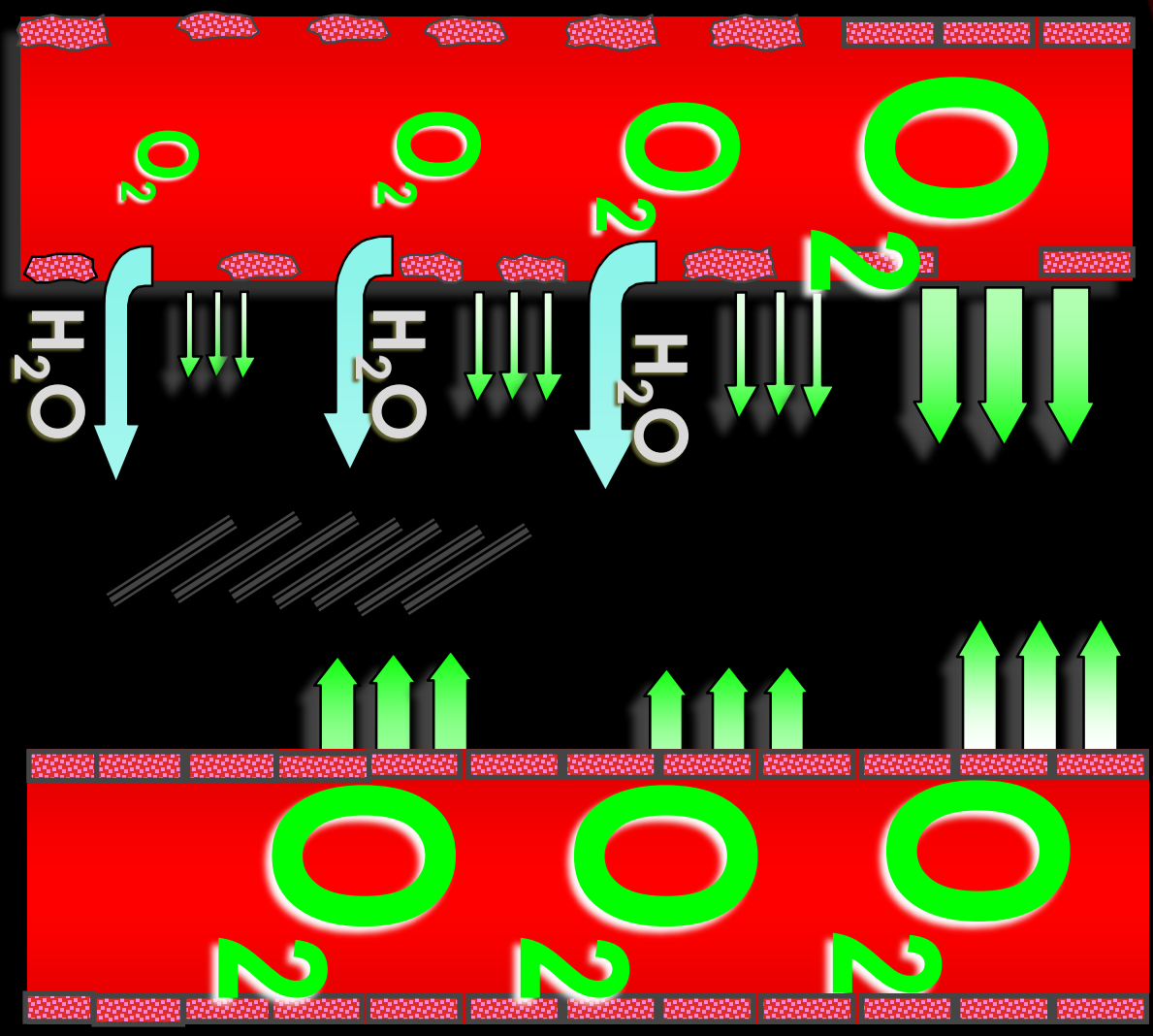



LaserFlow Doppler Variation
n=8 (20 min treatement)
% of control values
250
200
150
100
50
0
0,004
**
0,001
ns
0,03
**
Normative
Patient
MLD

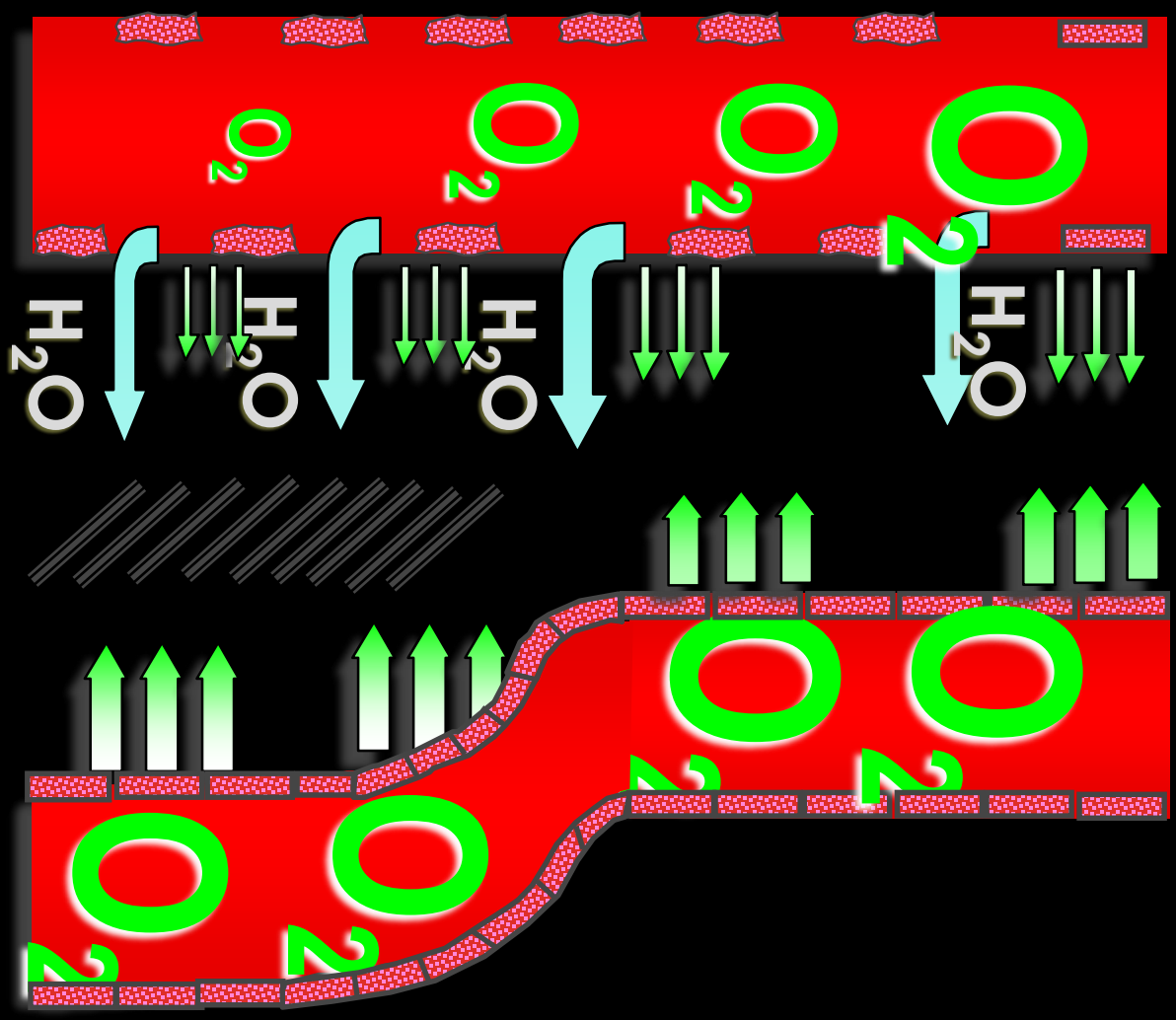

ORIGINAL MOTION PICTURE SOUNDTRACK
ROBIN HOOD
PRINCE OF THIEVES
COMPOSED AND CONDUCTED BY MICHAEL KAMEN

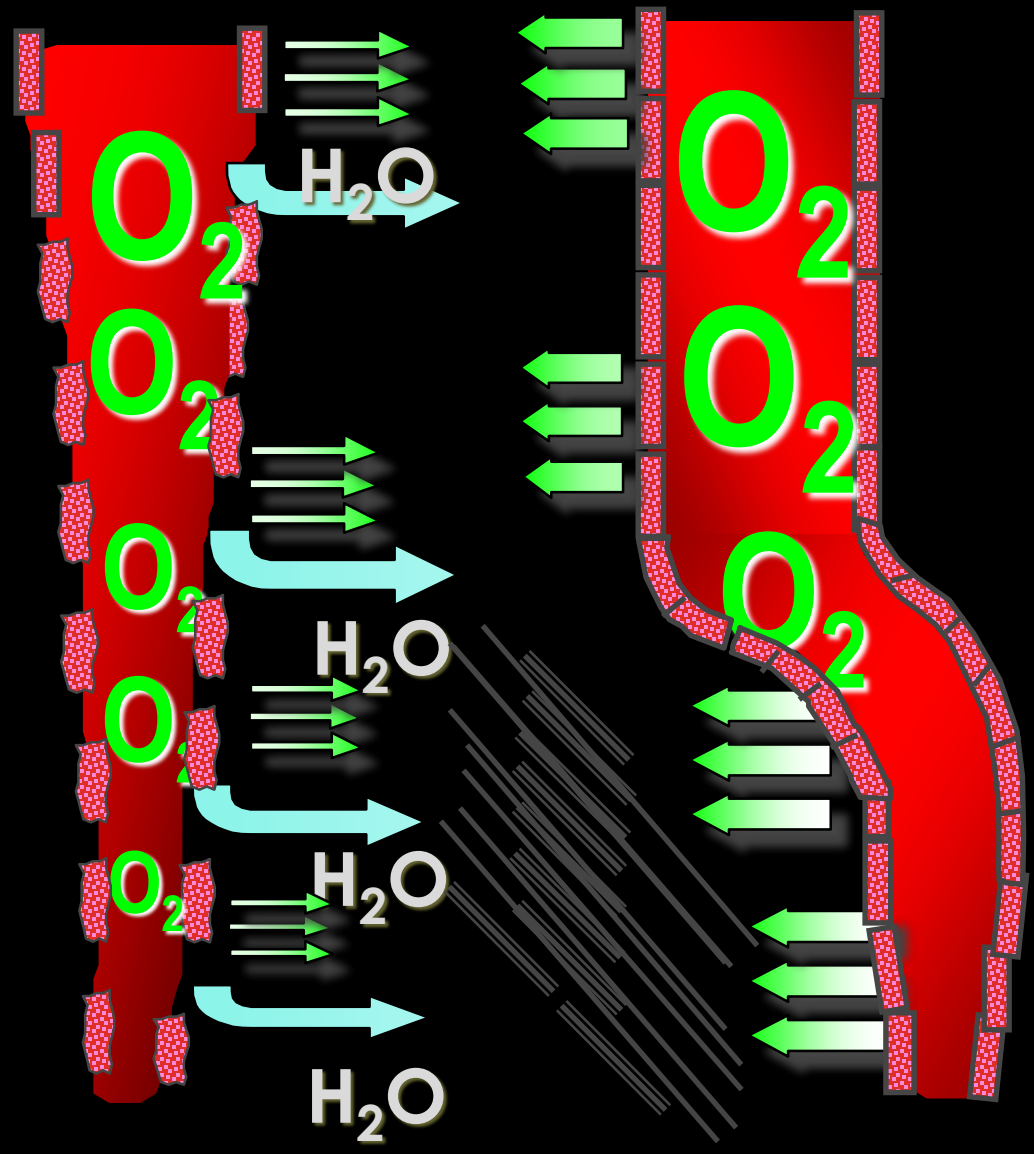

O_2
O_2
Capillaire
Capillary
Cellules
Cells


O2
O2
O2
O2
O2
O2
O2

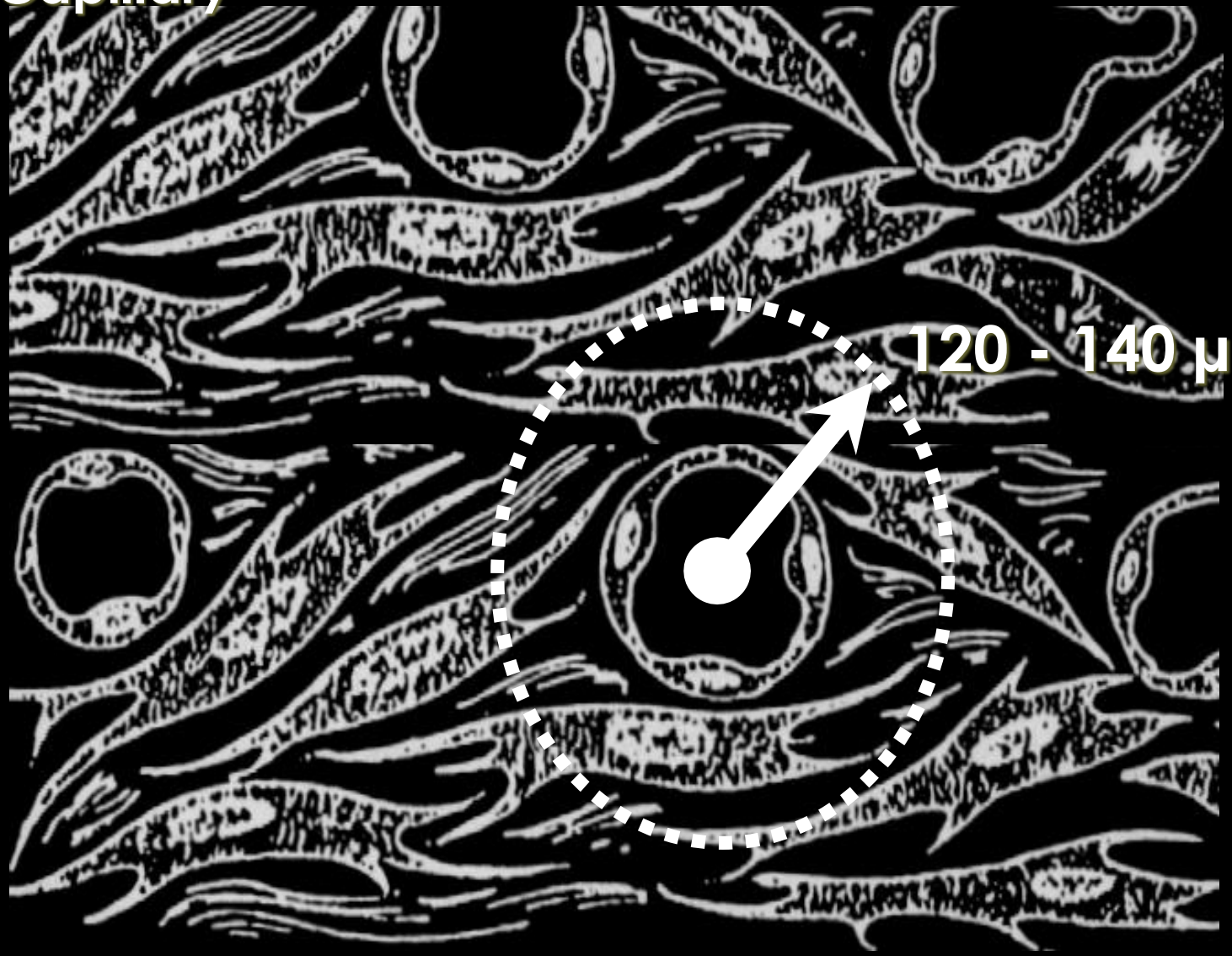

O2
O2
O2
O2
H2O
H2O
H2O

O2
O2
O2


O2
O2
O2
O2
H2O
H2O
H2O
H2O
O2
O2
O2
O2
O2

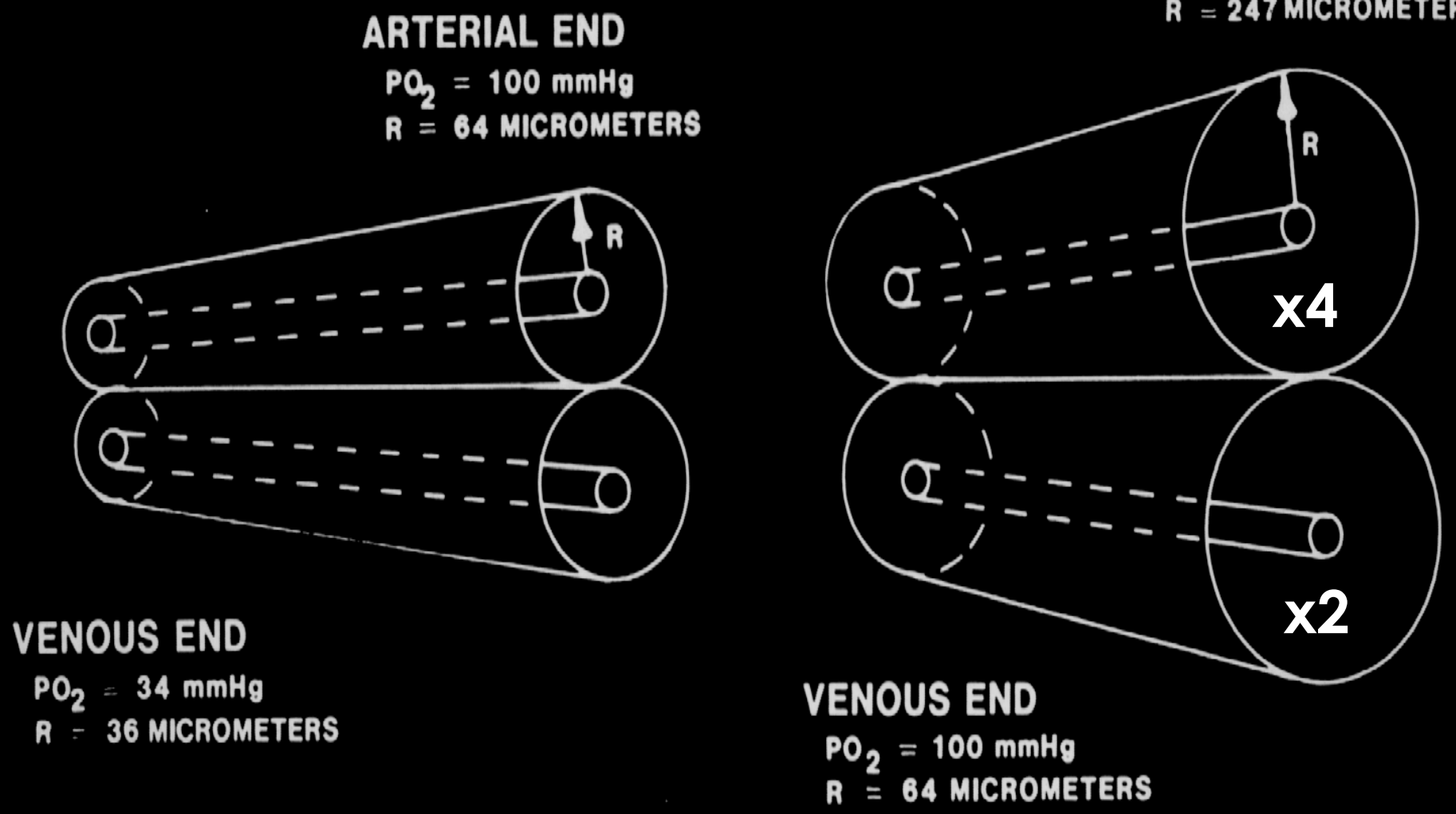

O_2
H_2O
O_2
O_2
H_2O
O_2
H_2O
O_2
H_2O
O_2
O_2
O_2

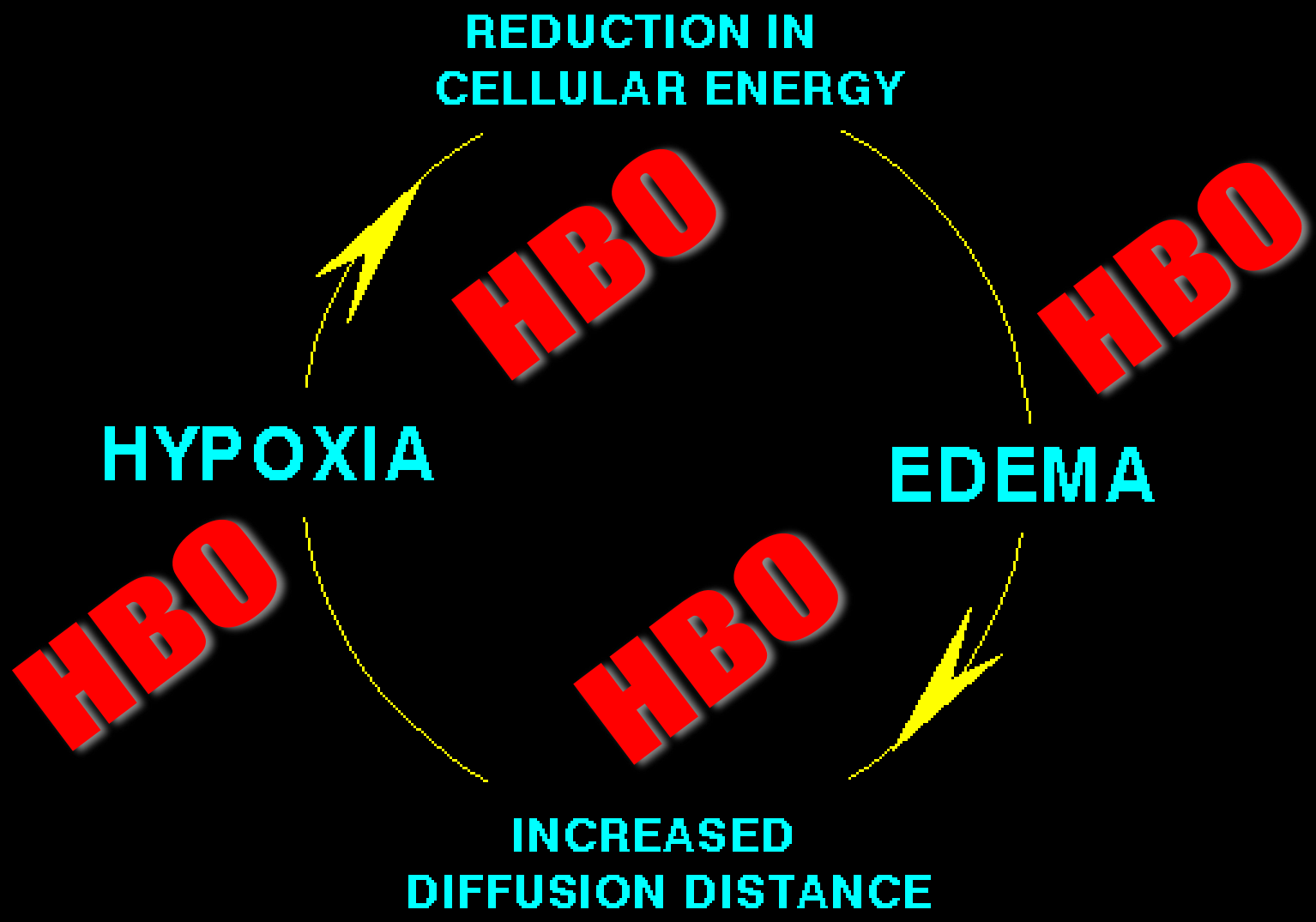
Maximum O_2 Diffusion Distance From a Functional Capillary



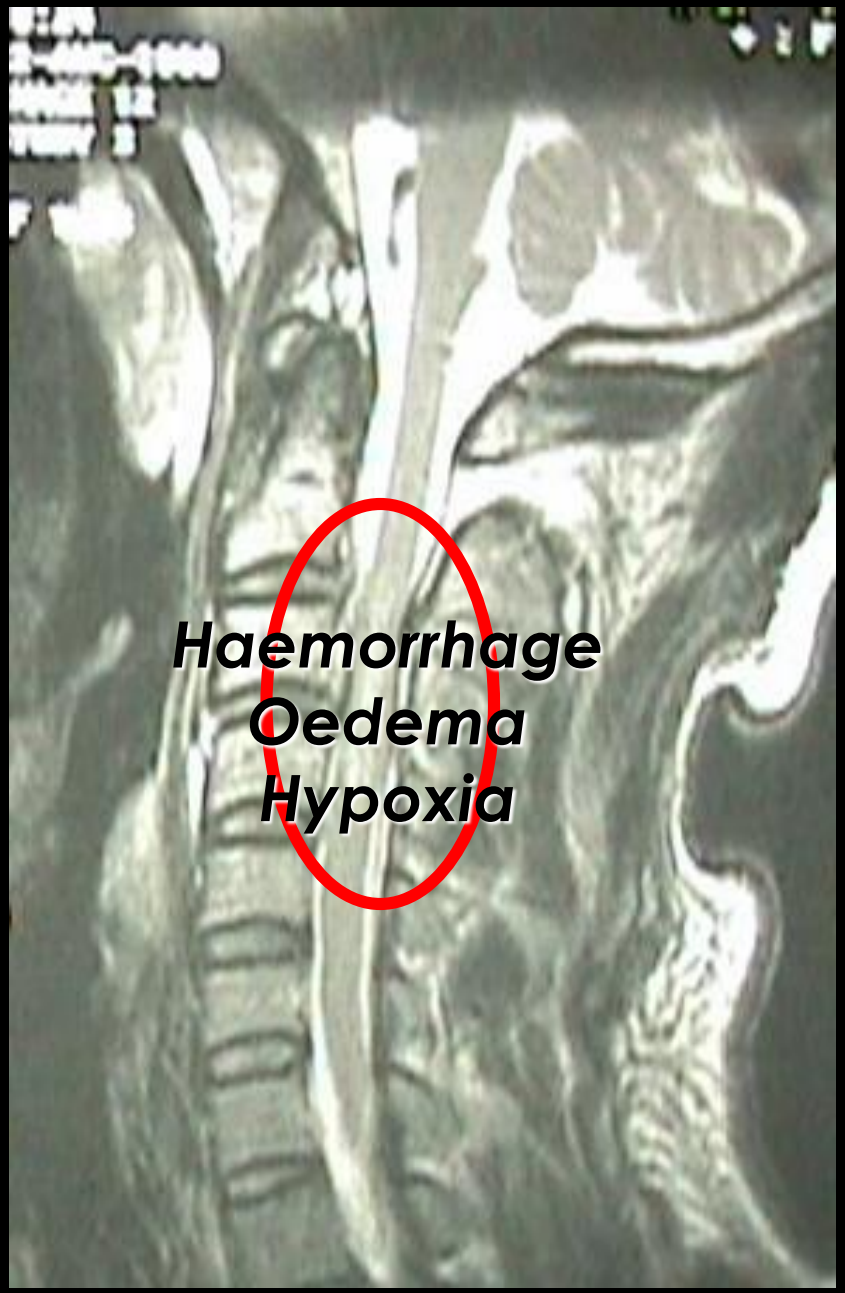
Silver 1976

Kroch's Mathematical Model (1919)

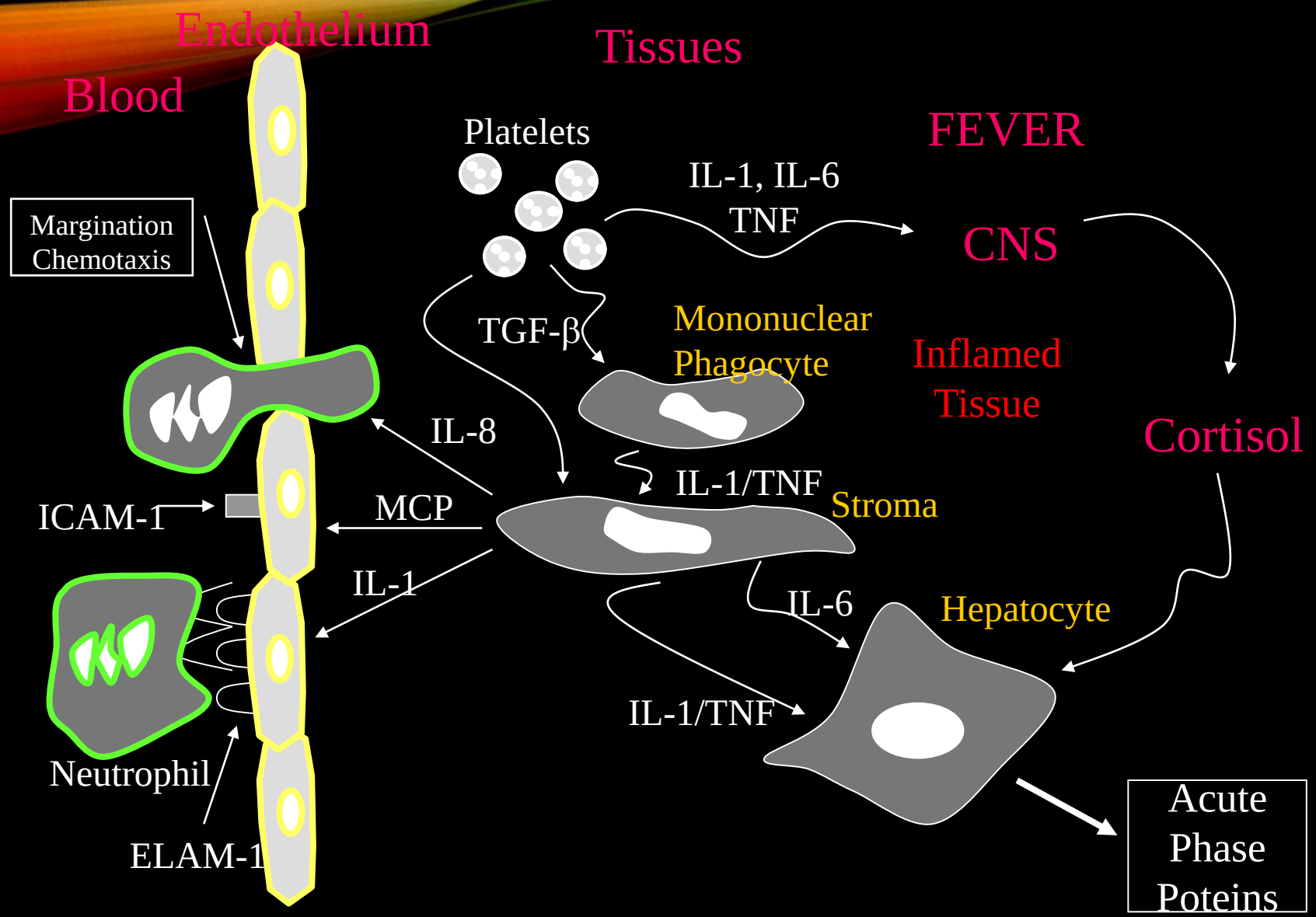


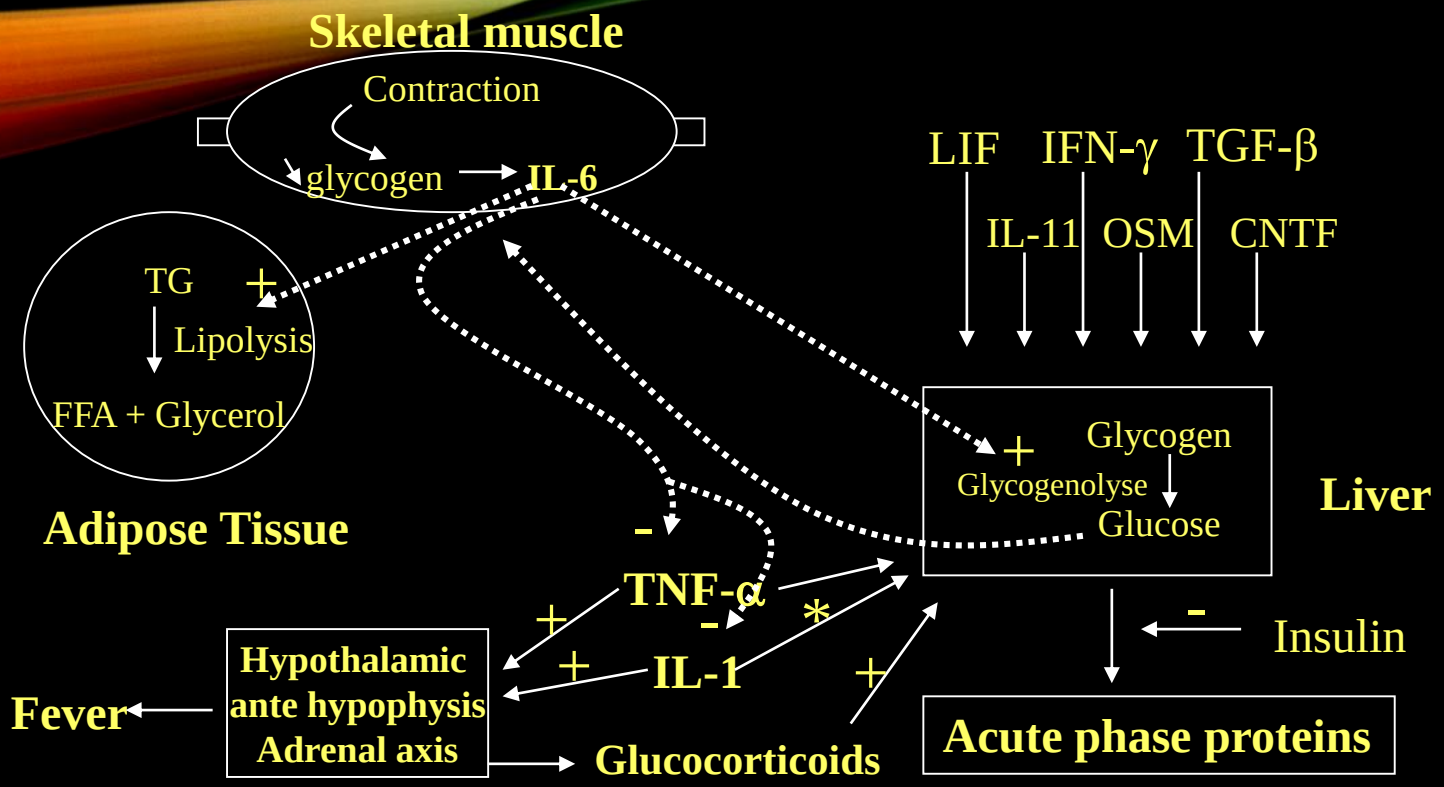

REDUCTION IN
CELLULAR ENERGY
HBO
HBO
HYPOXIA
EDEMA
HBO
HBO
HBO
INCREASED
DIFFUSION DISTANCE

SPINAL CORD INJURY




1. 5. 1999


Endothelium
Blood
Tissues
Platelets
FEVER
IL-1, IL-6
TNF
CNS
Margination
Chemotaxis
TGF-β
Mononuclear
Phagocyte
Inflamed
Tissue
Cortisol
IL-8
IL-1/TNF
Stroma
ICAM-1
MCP
IL-1
IL-6
Hepatocyte
IL-1/TNF
Neutrophil
ELAM-1
Acute
Phase
Poteins

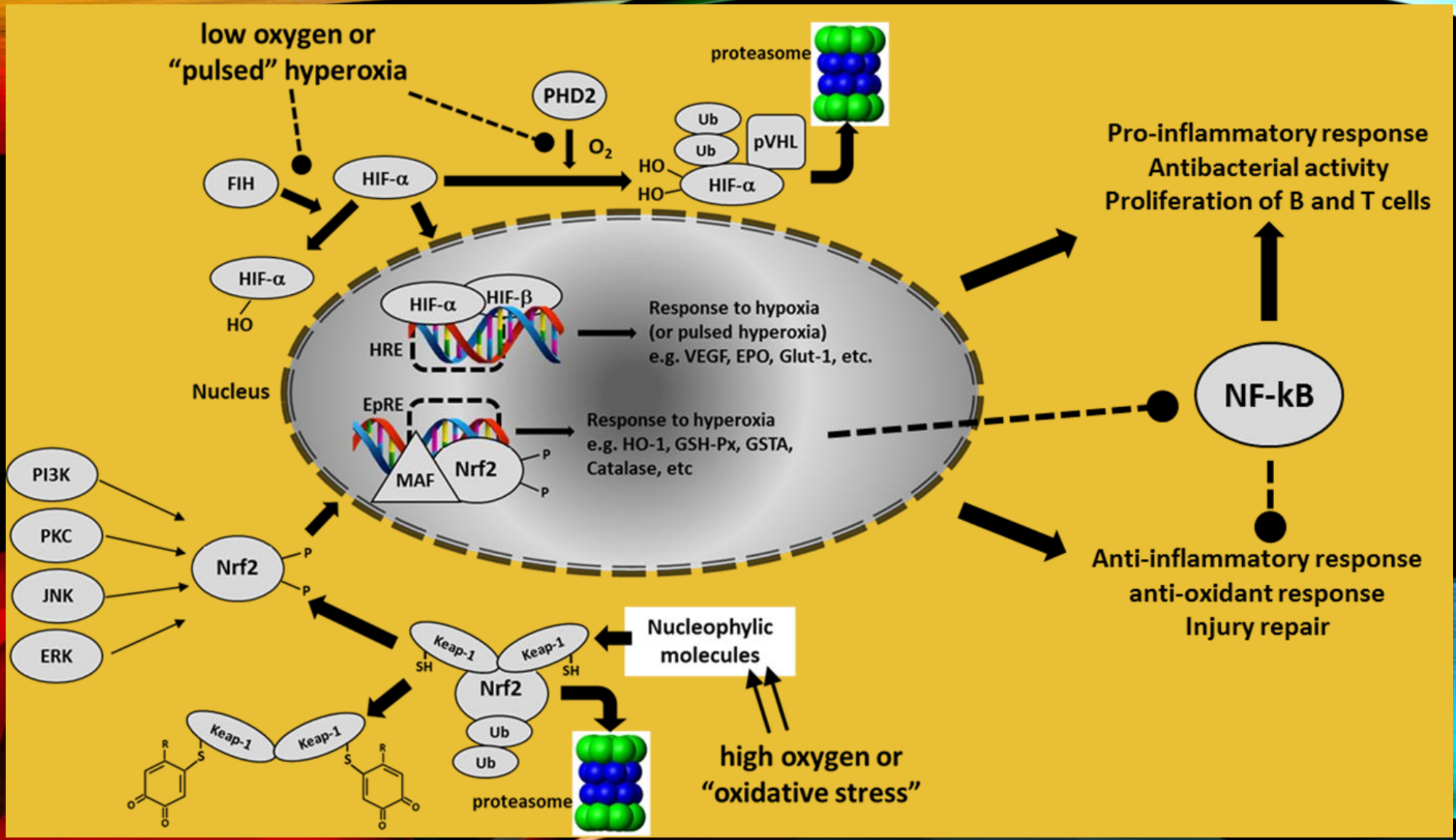


Complement Proteins	Coagulation Proteins	Proteinase Inhibitors	Metal binding Proteins	Acute Phase Reactants	Negative AP Reactants	Other Proteins
C2,C3,C4,	Fibrinogen	α1-antitrypsin	Haptoglobin	Serum Amyloid A	Albumin	α1-ac. Glycoprot.
C5,C9	Von Willebrand	α1-antitchimotrypsin	Hemopexin	C-reactive prot.	Pre-albumin	Heme oxygenase
Factor B		α2-antiplasmin	Ceruloplasmin	Serum amyloid P	Transferrin	Mannose-binding prot.
C1 Inhibitor		Heparin cofactor II	Mn SOD	component	ApoAI	Leukocyte prot.1
C4 binding prot.		Plasm. Activator			ApoAII	Lipoprotein
		Inhib.1			α2-Hsglycoprot.	Lipopolysaccharide
					Inter-α-trypsin inhib.	binding prot.
					Histidine rich glycoprot.	

* Increasing activity

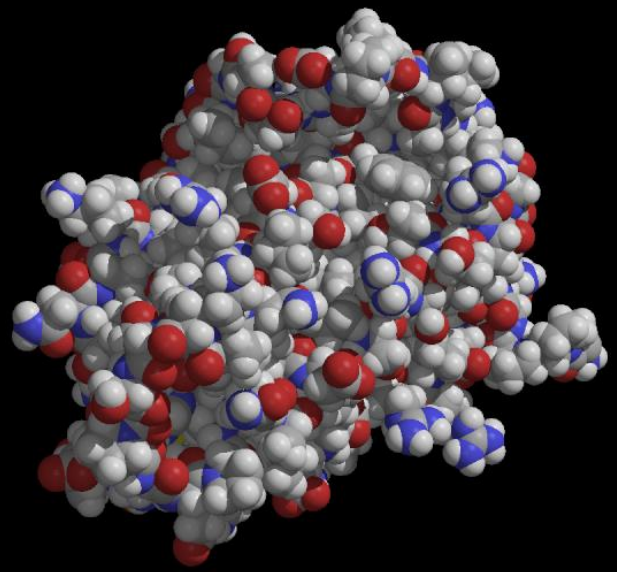
FOCUSING……

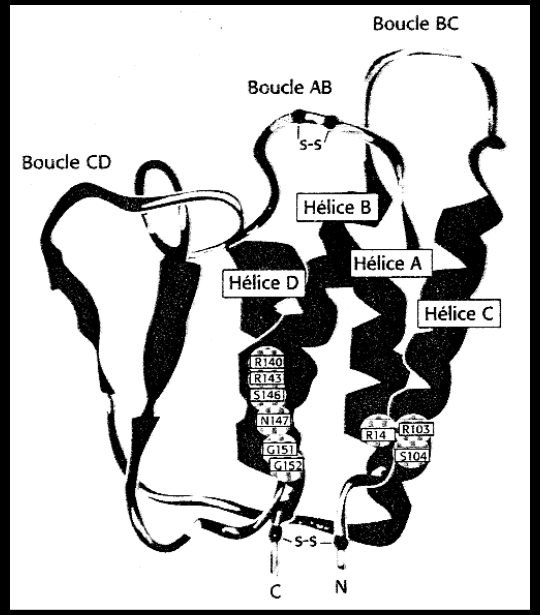
1991 GREG SEMENZA HIF-1ALPHA


low oxygen or
"pulsed" hyperoxia
PHD2
O_2
proteasome
Ub
Ub
pVHL
HO
HO
HIF-α
FIH
HIF-α
HO
HIF-α
HIF-β
HRE
Response to hypoxia
(or pulsed hyperoxia)
e.g. VEGF, EPO, Glut-1, etc.
Nucleus
EpRE
MAF
Nrf2
P
P
Response to hyperoxia
e.g. HO-1, GSH-Px, GSTA,
Catalase, etc
Pro-inflammatory response
Antibacterial activity
Proliferation of B and T cells
NF-kB
Anti-inflammatory response
anti-oxidant response
Injury repair
PI3K
PKC
JNK
ERK
Nrf2
P
P
Keap-1
Keap-1
SH
SH
Nrf2
Ub
Ub
proteasome
Nucleophylic
molecules
high oxygen or
"oxidative stress"
Keap-1
Keap-1
R
S
S
R
O
O
O

INTRODUCTION

- Erythropoietin (EPO) regulates RBC homeostasis but also known as antiapoptotic neuroprotective agent
- Polypeptid (cytokine) hormone (Bazan, 1990)

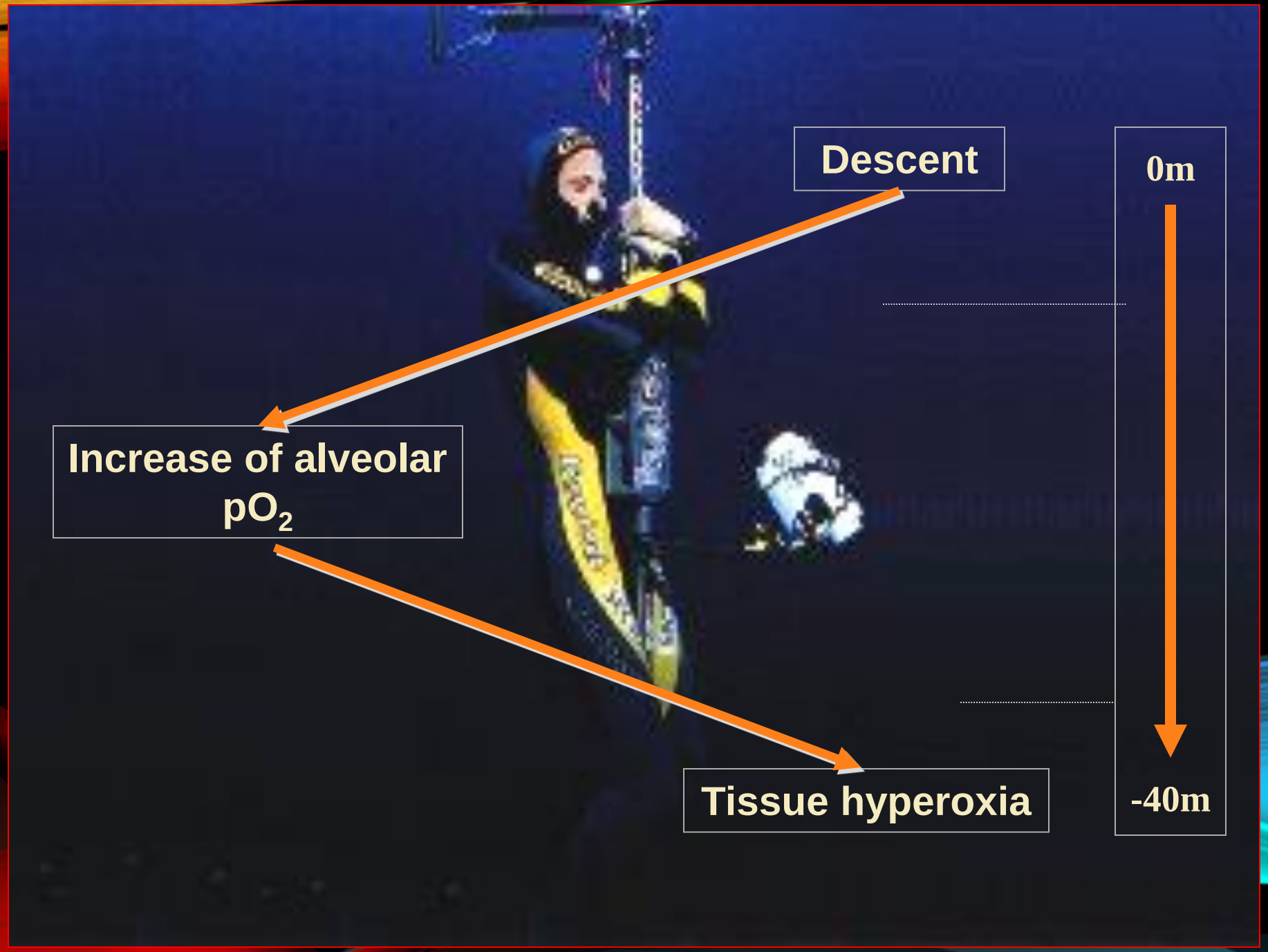


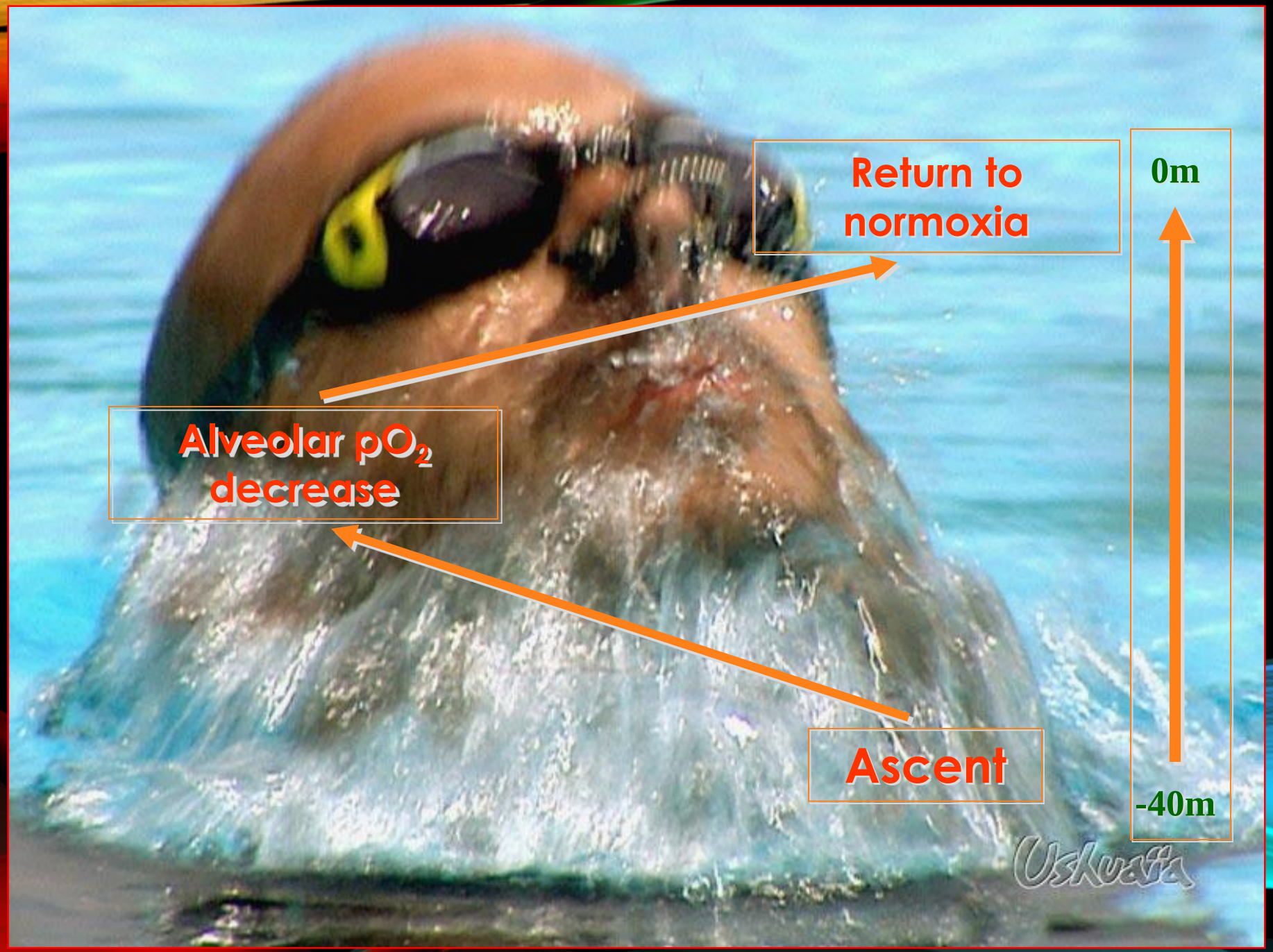


- Production in renal proximal tubular cell, in response to tissue hypoxia (Goldwasser, 1957)
- Normal plasma values : 5 - 25 mU/ml
- Circadian rhythm: litterature discordances (Wide 1989, Cahan 1992, Miller 1981, Cotes & Brozovic 1982, Klausen 1993)

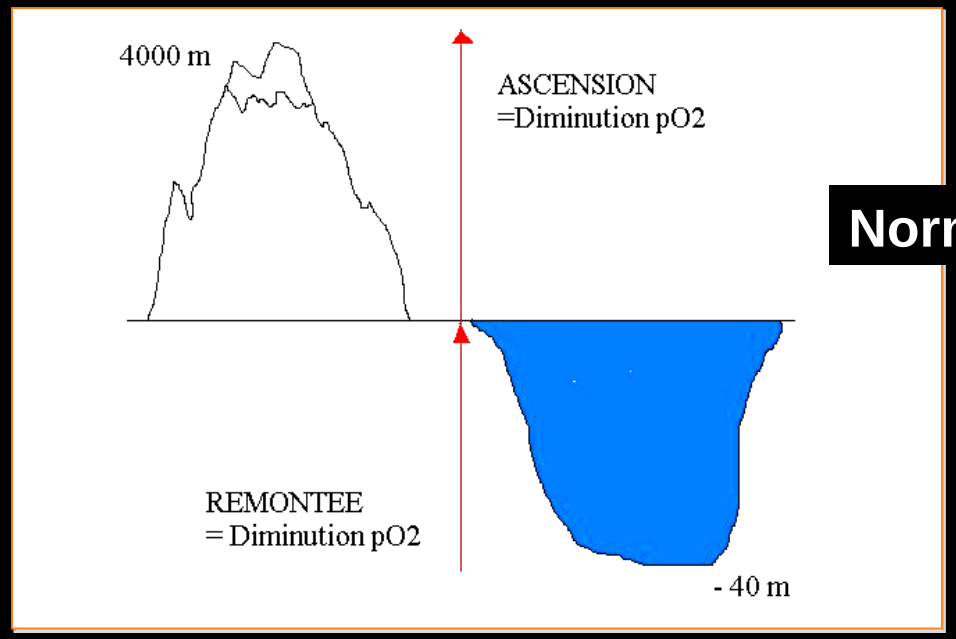
POSSIBLE OTHER STIMULUS ?

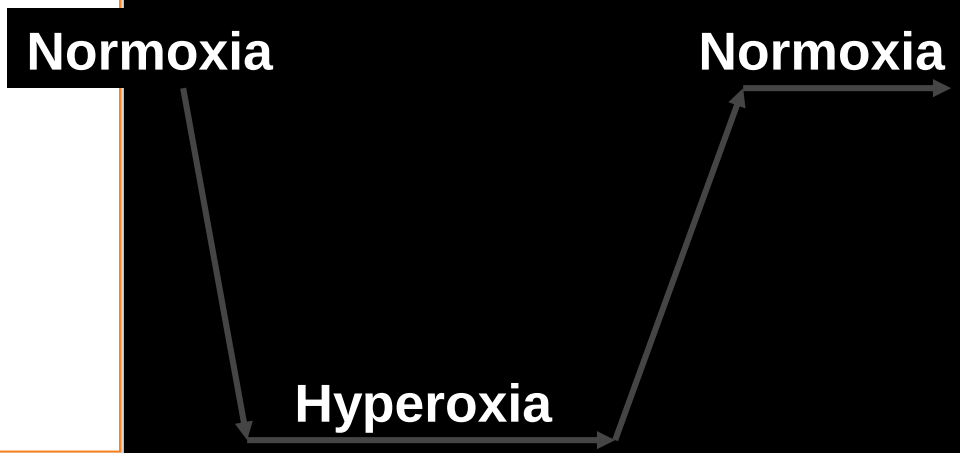
- Serum EPO measurements in apnea divers after 3 dives to -40 m (1999 Malta EUBS Meeting)
- [EPO] markedly elevated !
- Hypothesis: tissular pO_2 variation as a stimulus for EPO production


Descent
0m
Increase of alveolar pO_2
Tissue hyperoxia
-40m


Return to normoxia
Alveolar pO_2 decrease
Ascent
0m
-40m

CONCEPT OF "RELATIVE HYPOXIA"

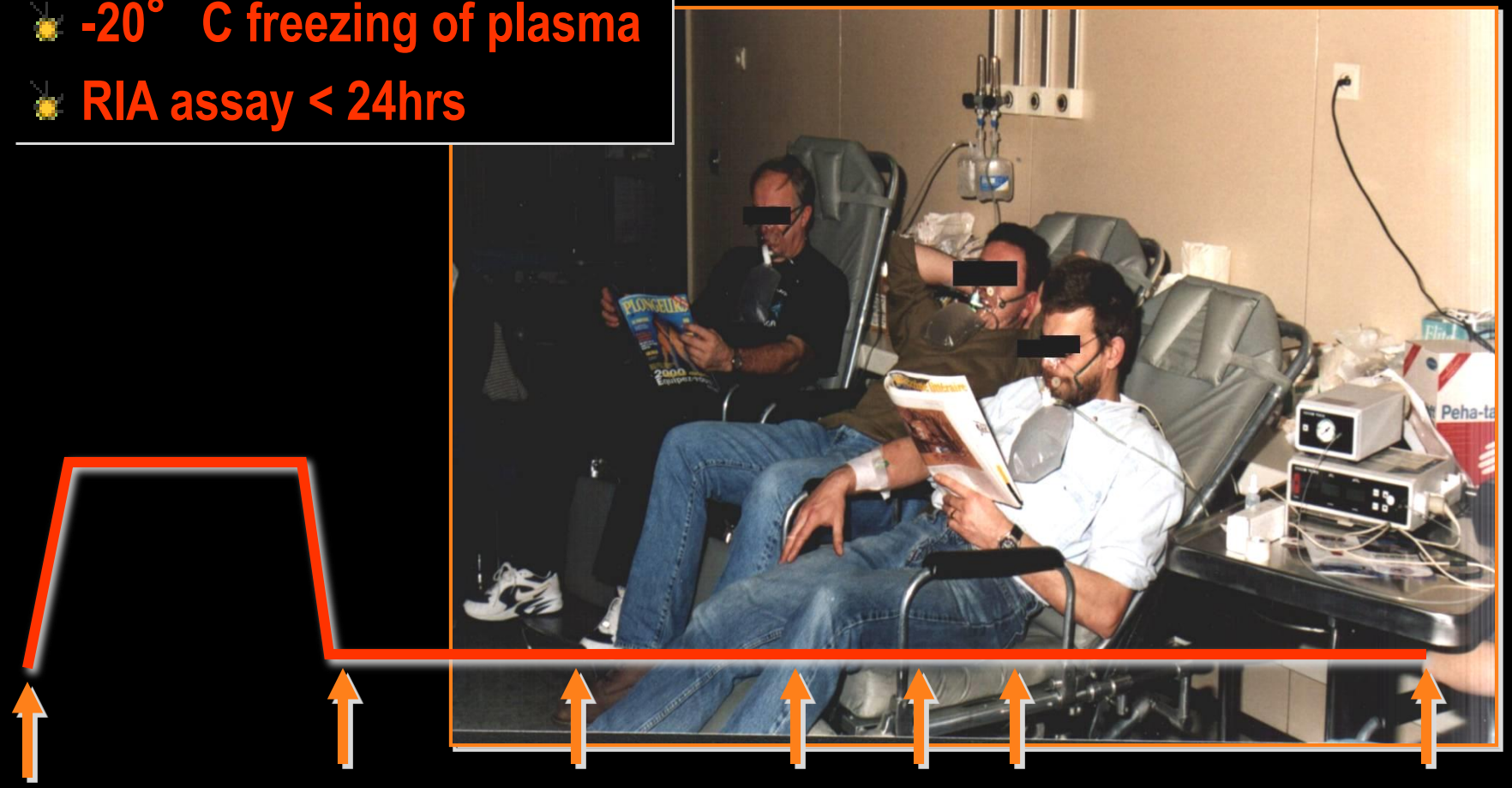




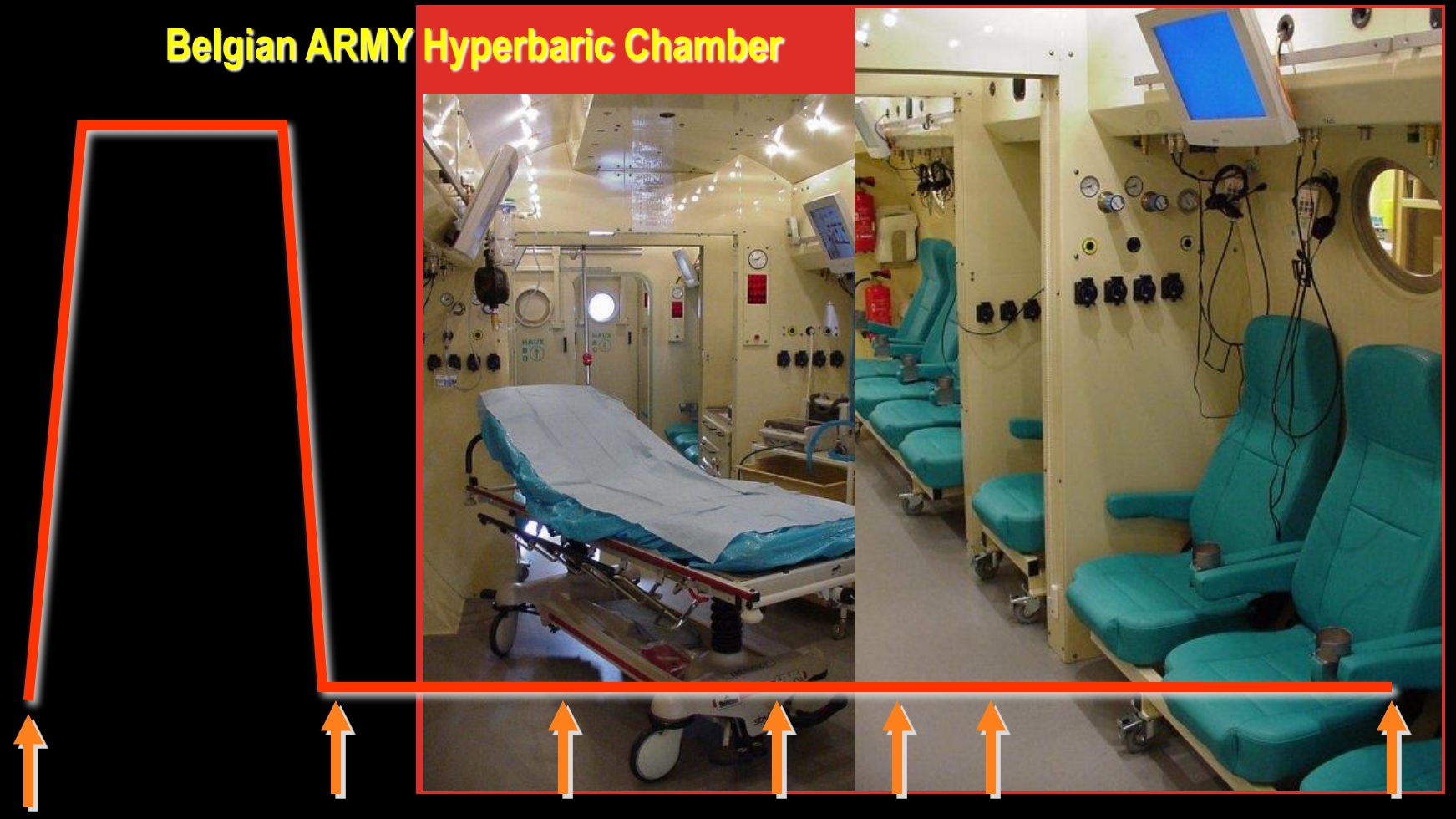
- Tissue N_2-O_2 balance : increase in relative N_2 content
- "Trigger time": at least 45 minutes = sustained change

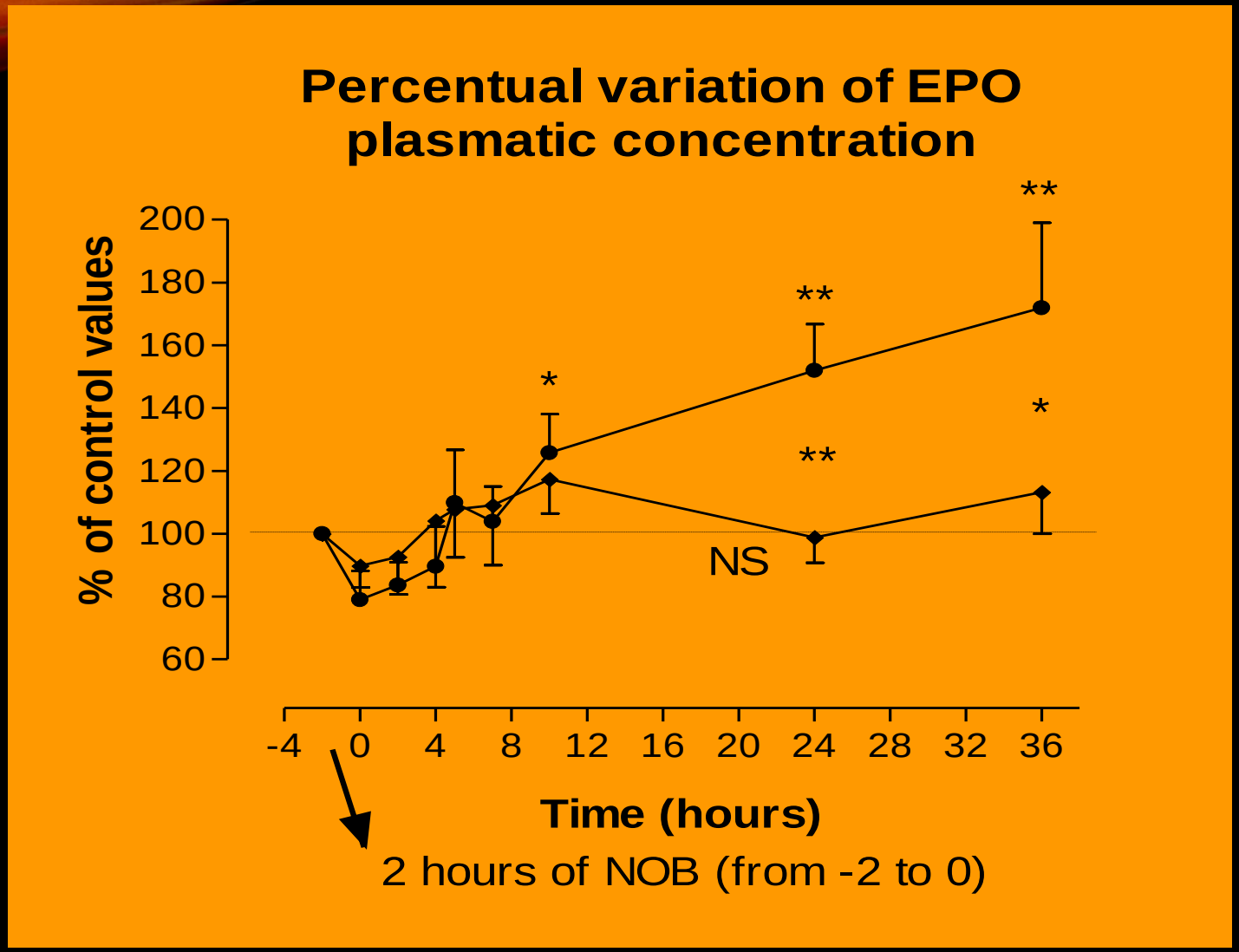
NORMOBARIC HYPEROXIA

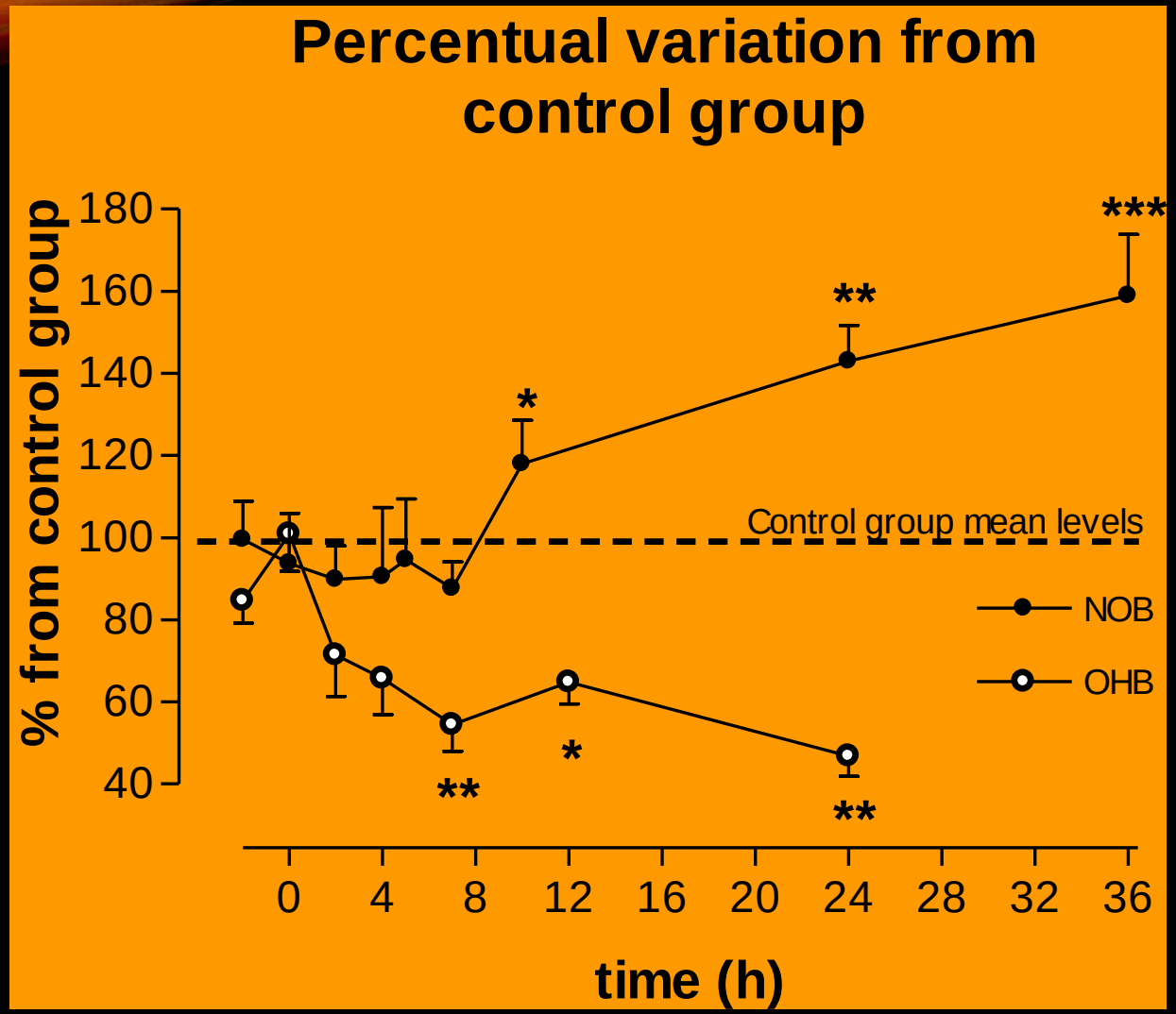
- 2cc blood samples
- -20° C freezing of plasma
- RIA assay < 24hrs

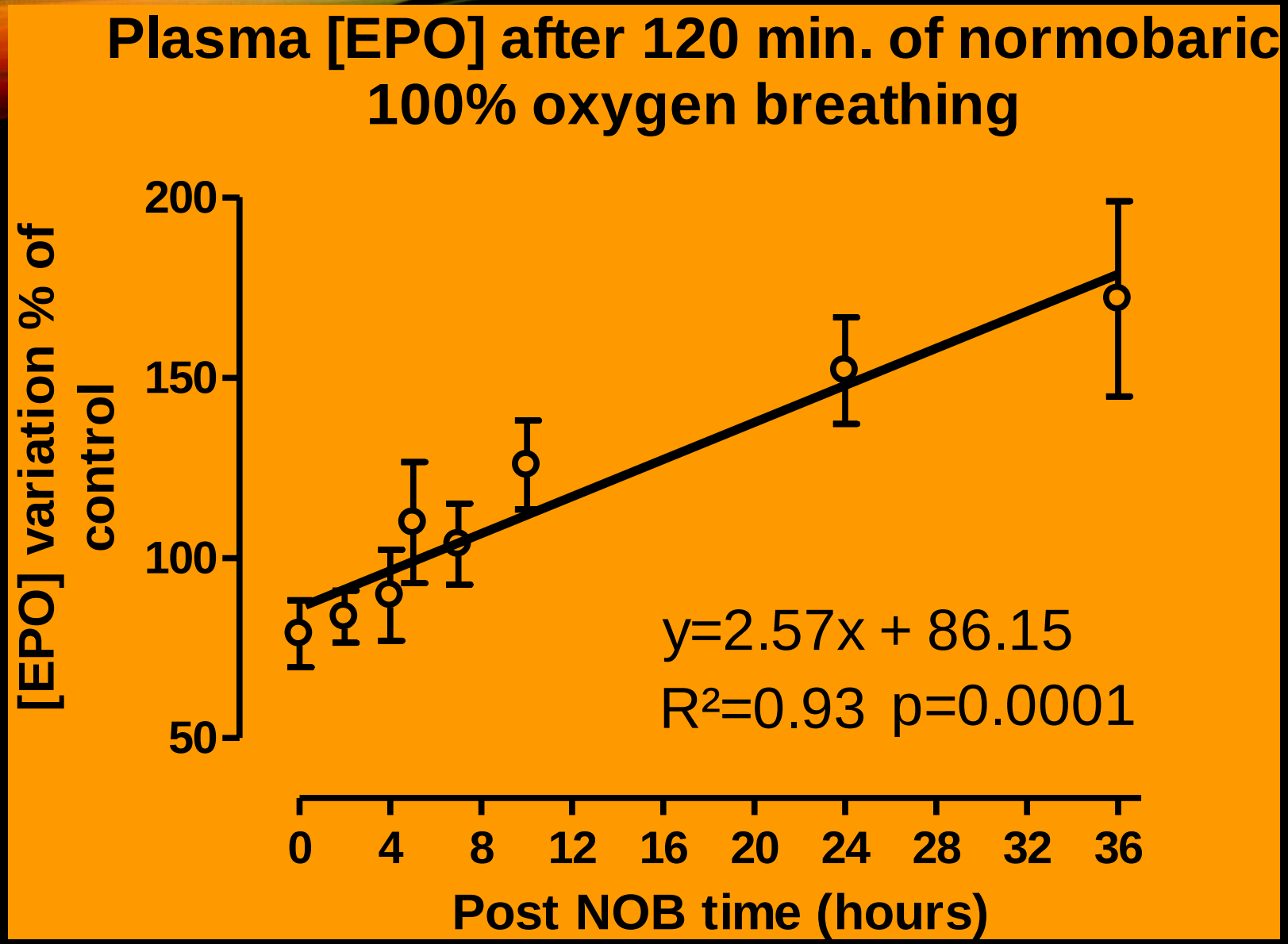


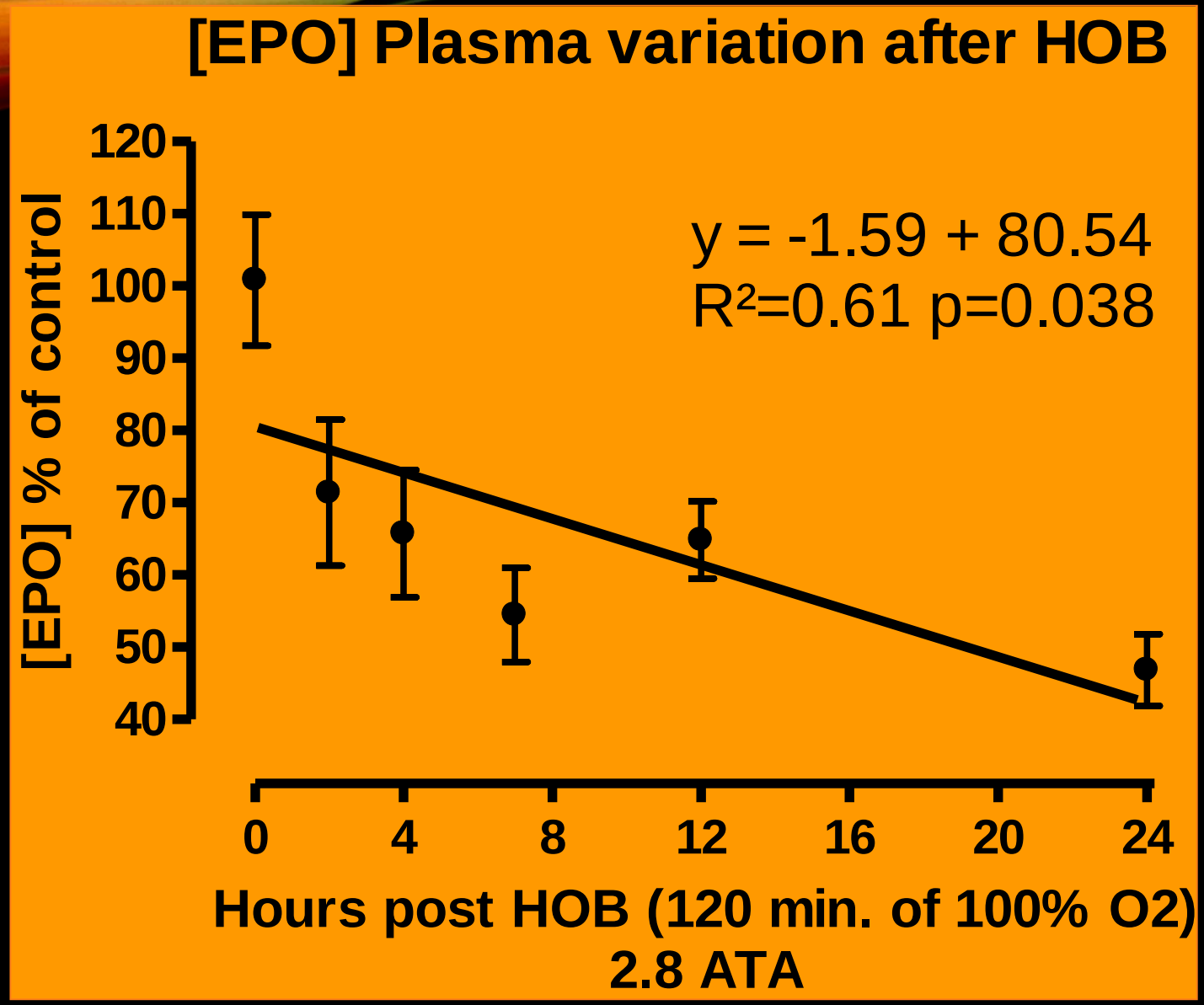
HYPERBARIC HYPEROXIA




Percentual variation of EPO plasmatic concentration
% of control values
200
180
160
140
120
100
80
60
-4
0
4
8
12
16
20
24
28
32
36
Time (hours)
*
**
**
*
**
NS
2 hours of NOB (from -2 to 0)


Percentual variation from control group
% from control group
180
160
140
120
100
80
60
40
0
4
8
12
16
20
24
28
32
36
time (h)
Control group mean levels
NOB
OHB
*
**
***
**
*
**


Plasma [EPO] after 120 min. of normobaric 100% oxygen breathing
[EPO] variation % of control
200
150
100
50
y=2.57x + 86.15
R²=0.93 p=0.0001
0
4
8
12
16
20
24
28
32
36
Post NOB time (hours)

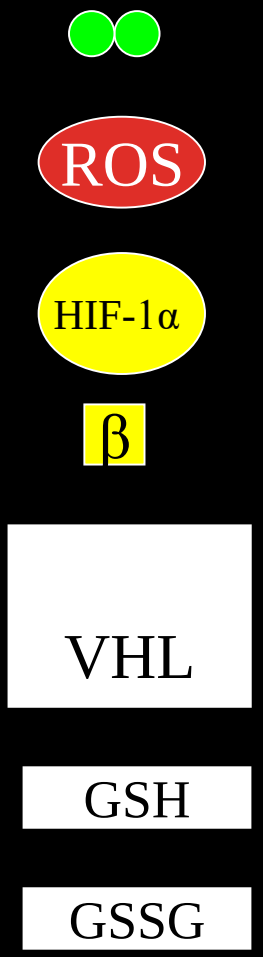

[EPO] Plasma variation after HOB
[EPO] % of control
120
110
100
90
80
70
60
50
40
y = -1.59 + 80.54
R²=0.61 p=0.038
0
4
8
12
16
20
24
Hours post HOB (120 min. of 100% O2)
2.8 ATA

Serum erythropoietin levels in healthy humans after a short period of normobaric and hyperbaric oxygen breathing: the "normobaric oxygen paradox"

Costantino Balestra, Peter Germonpré, Jacques R. Poortmans and Alessandro Marroni

Journal of Applied Physiology 100:512-518, 2006. First published Oct 20, 2005;
doi:10.1152/japplphysiol.00964.2005

- HERE ARE THE ACTORS

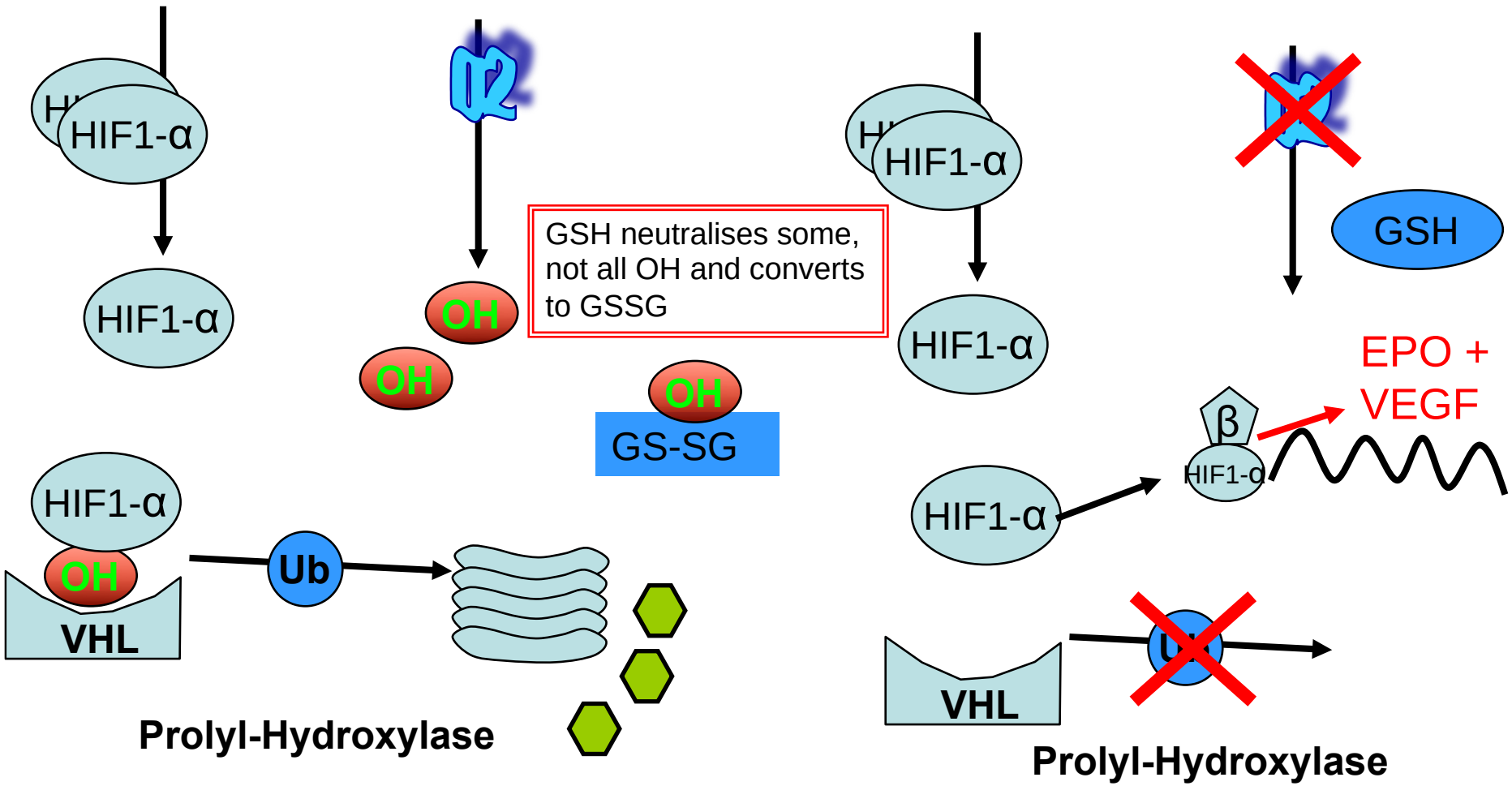


Normal situations

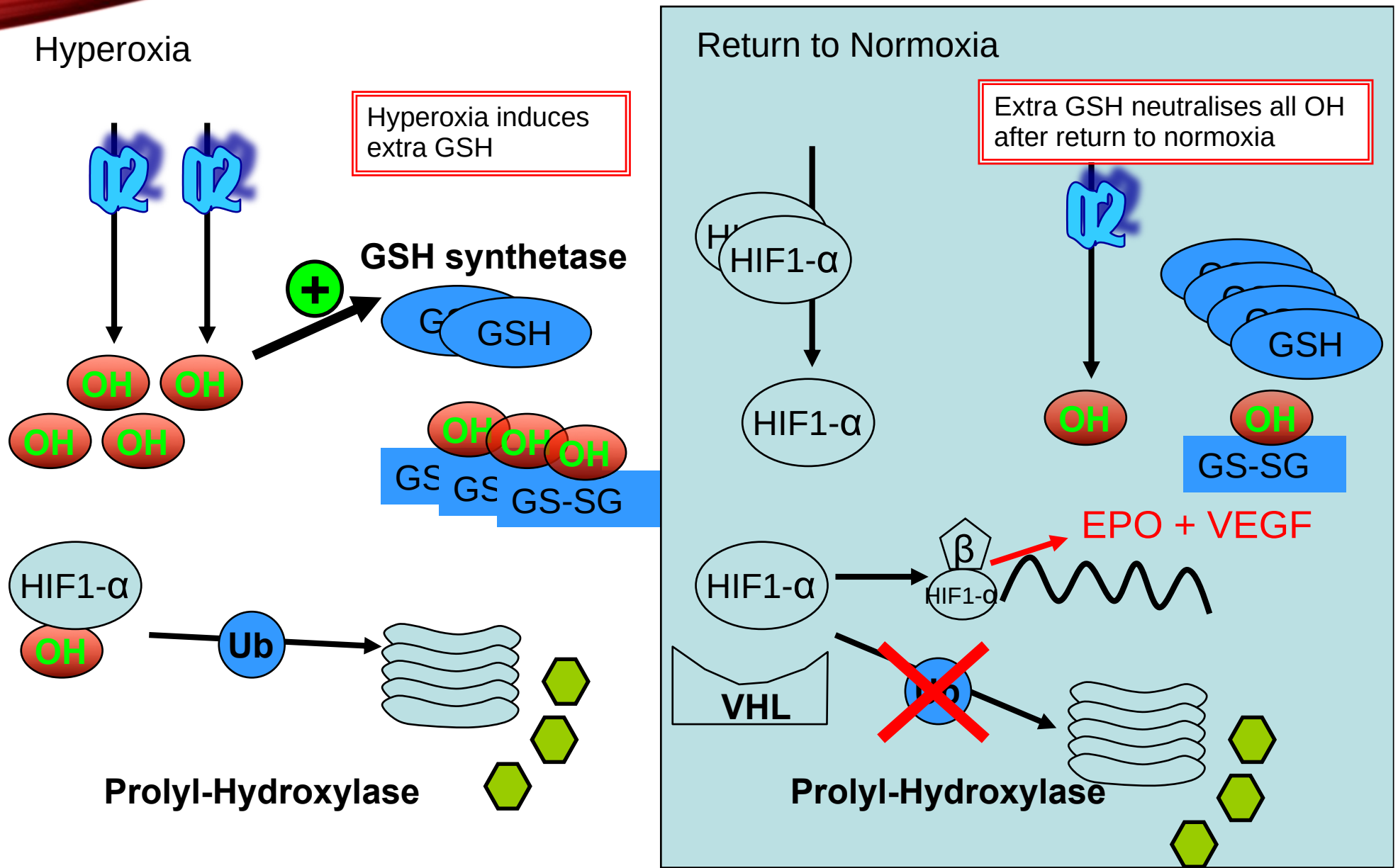
Normoxia

Hypoxia

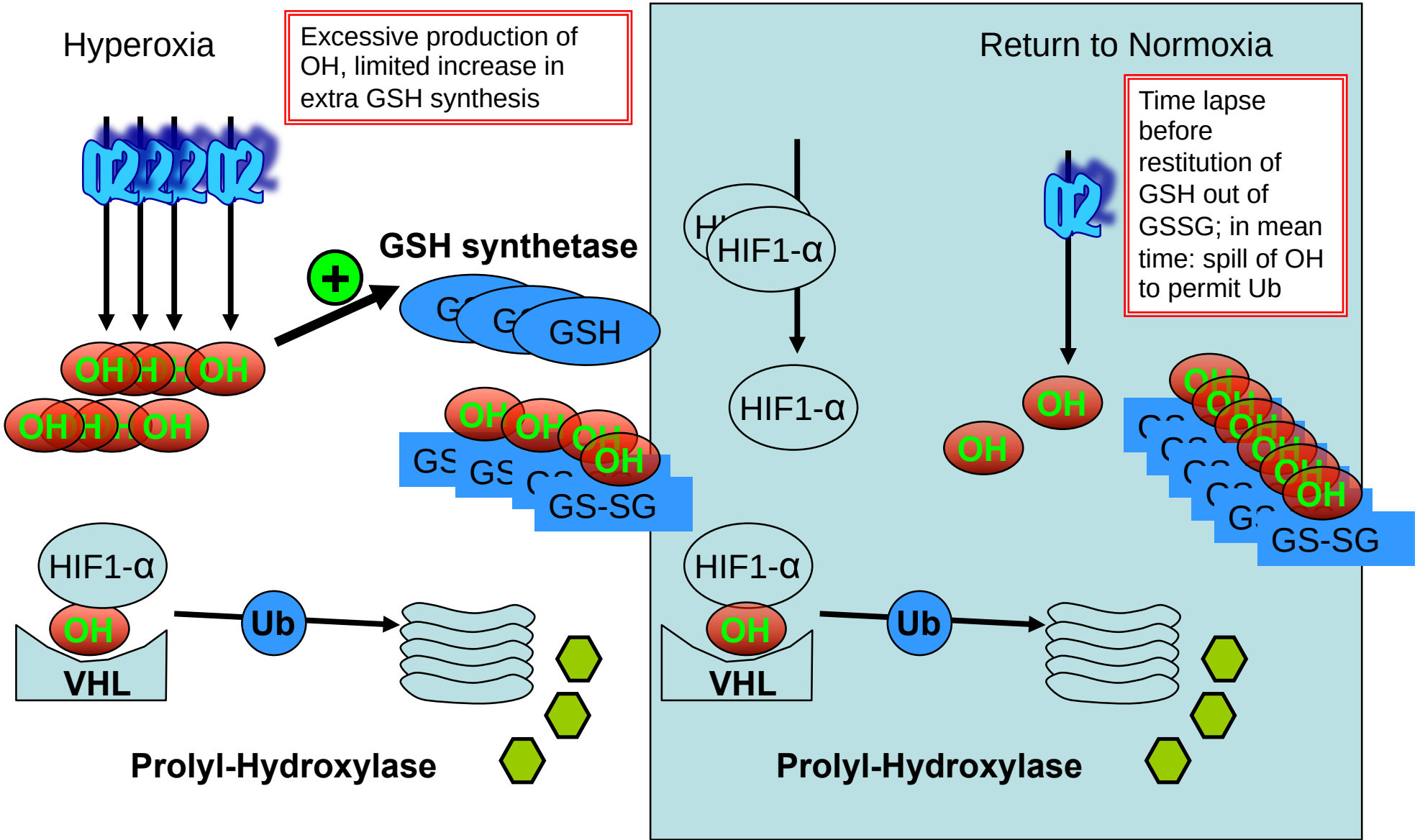
Extreme situation ! In less severe hypoxia, GSH neutralises all of the OH



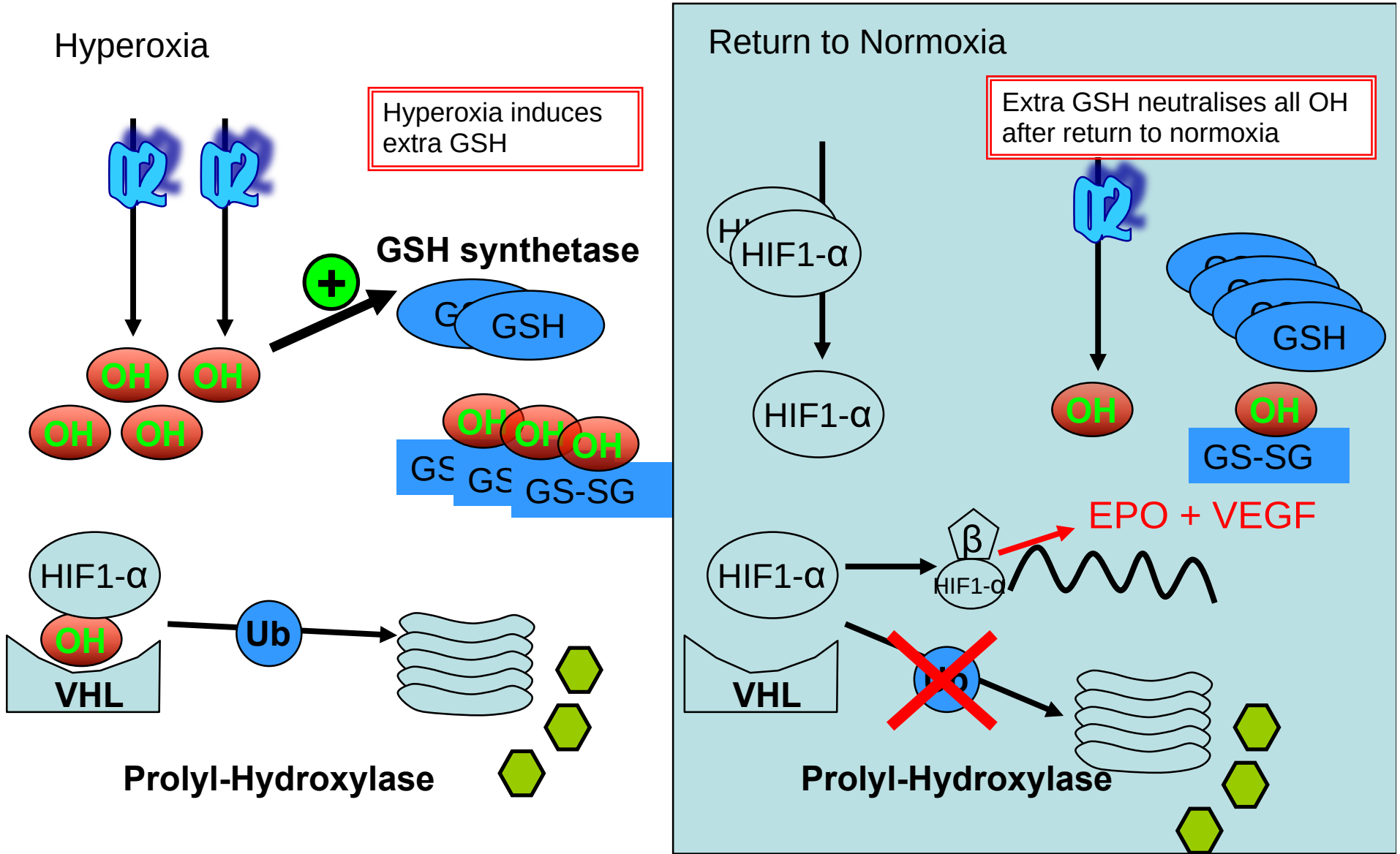
Normobaric hyperoxia



Hyperbaric hyperoxia

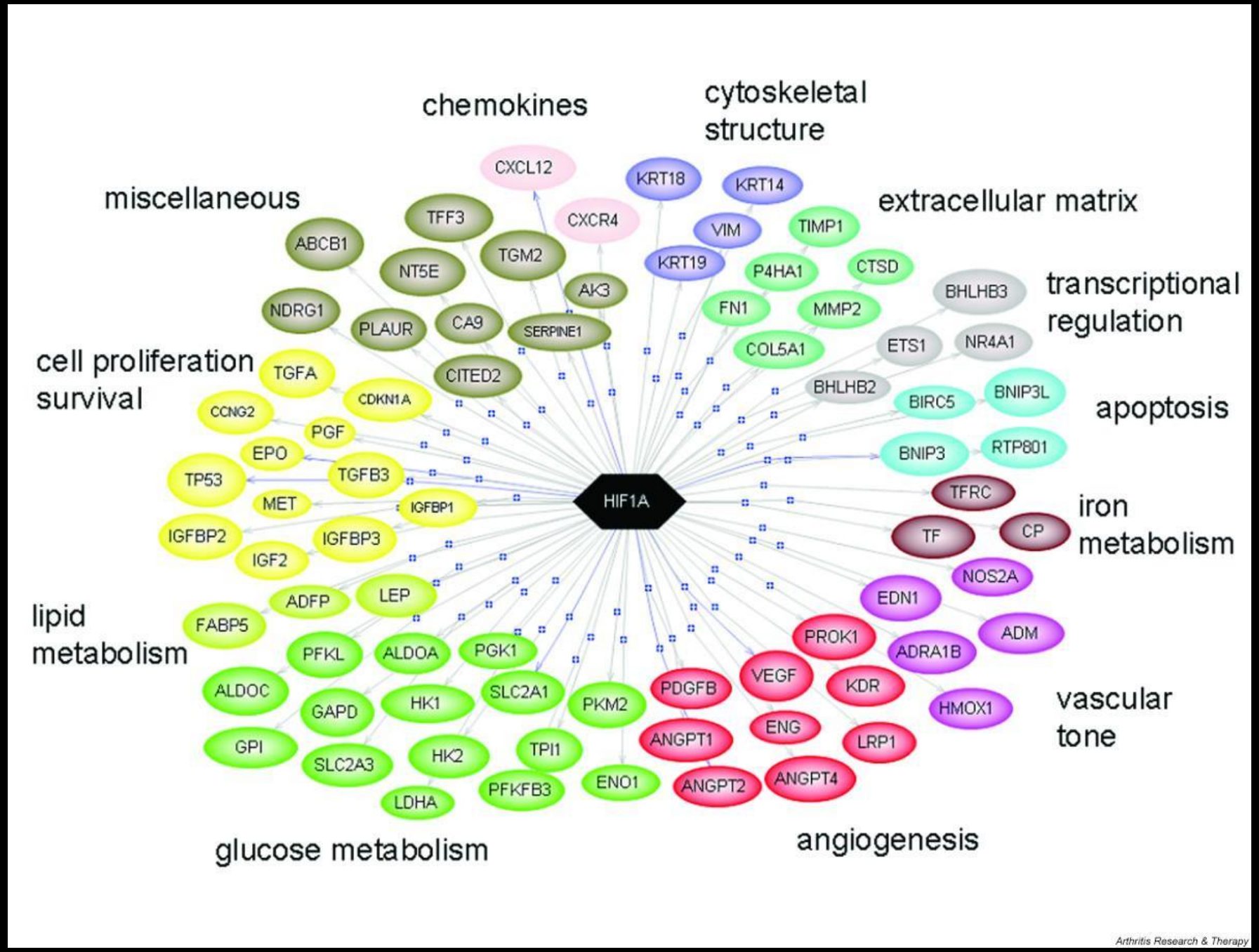


Normobaric hyperoxia



ERYTHROPOIETIN EPO

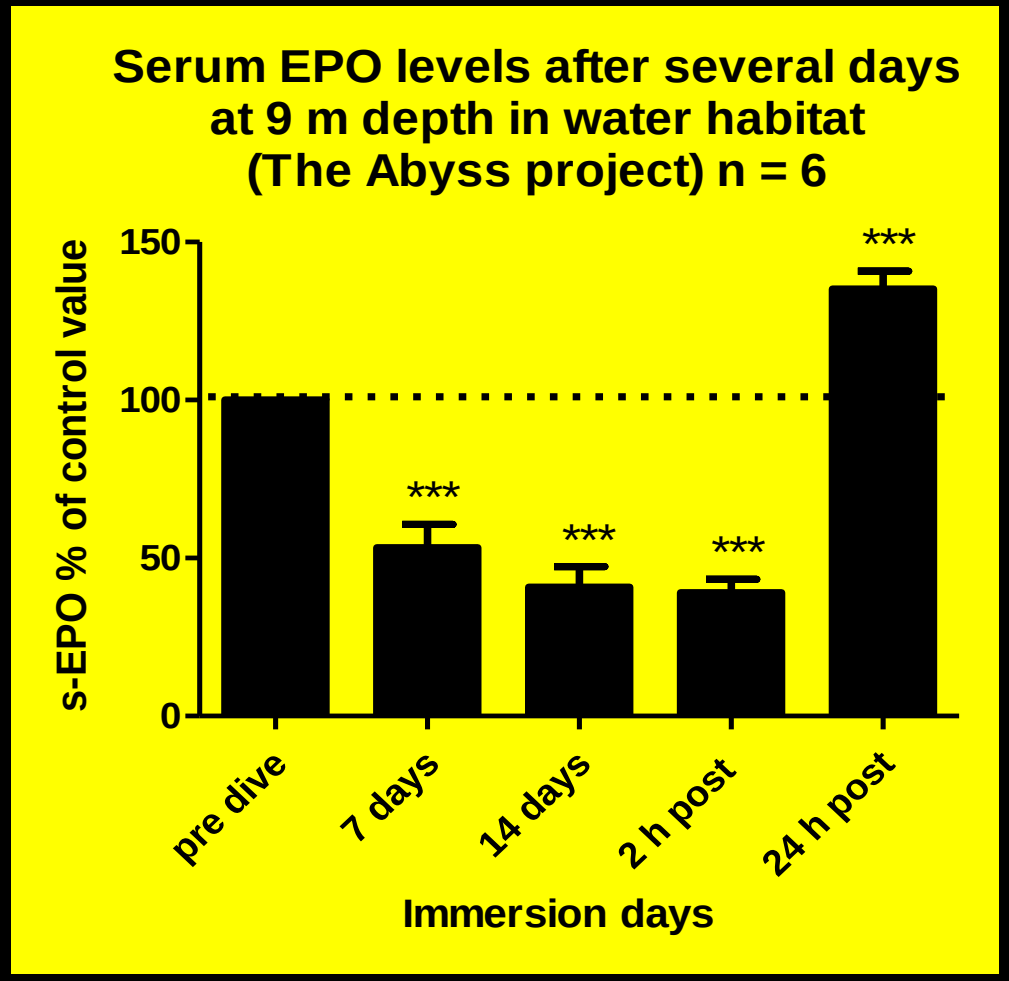
FOCUS?




BILIARDI-RAPONI
LATINA - ITALY
Claudio
FLIPPER
© Andrea Petrachi


EXPLORER TEAM
PELUCANO
© Andrea Petrachi

THE ABYSS PROJECT (PONZA ITALY)



Revelli L, Vagnoni S, D'Amore A, Di Stasio E, Lombardi CP, Storti G, Proietti R, Balestra C & Ricerca BM. (2013). EPO modulation in a 14-days undersea scuba dive. *Int J Sports Med* **34,** 856-860.

EPO Modulation in a 14-Days Undersea Scuba Dive

Authors: L. Revelli[1], S. Vagnoni[2], A. D'Amore[1], E. D. Stasio[3], C. P. Lombardi[1], G. Storti[4], R. Proietti[2], C. Balestra[5], B. M. Ricerca[6]

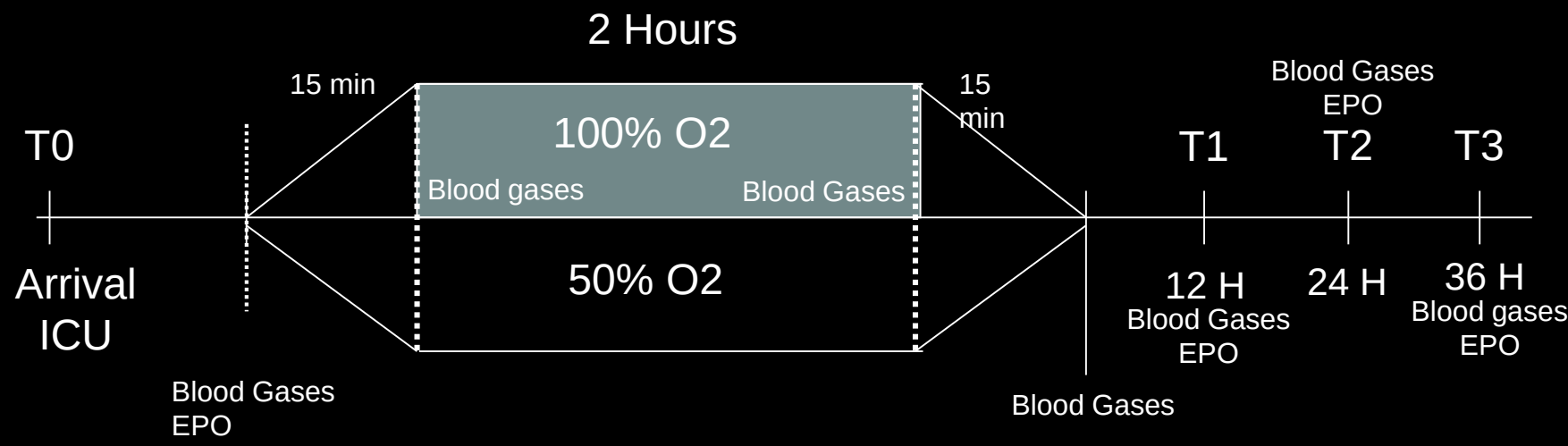
Affiliations: Affiliation addresses are listed at the end of the article

Key words
- erythropoietin (EPO)
- hyperbarism
- hyperoxia
- scuba dive
- reactive oxygen species (ROS)
- normobaric oxygen paradox (NOP)

Abstract

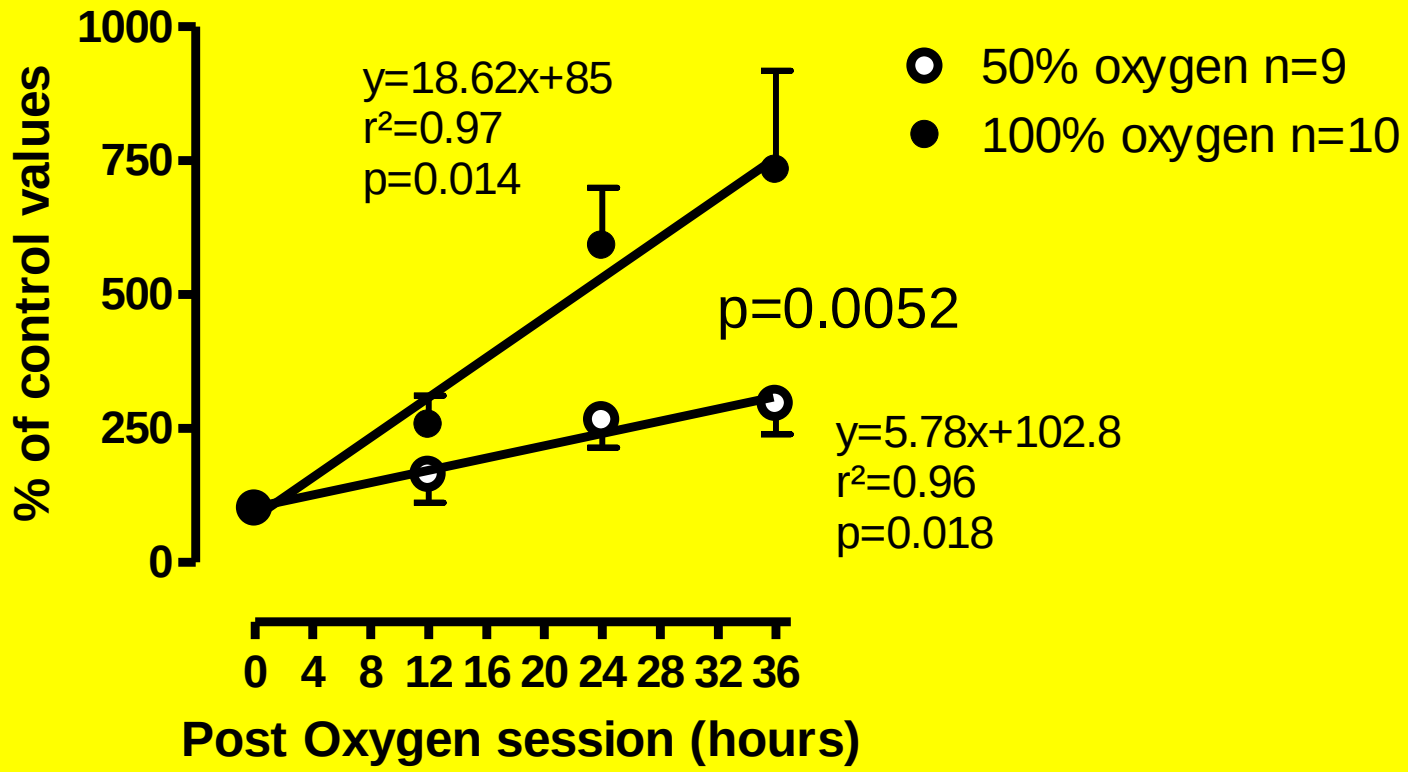
Erythropoiesis is affected during deep saturation dives. The mechanism should be related to a downregulation of serum Erythropoietin (s-EPO) concentration or to a toxic effect of the hyperbaric hyperoxia. We evaluated s-EPO and other haematological parameters in 6 scuba divers before, during and after a 14-days Guinness saturation dive (8–10 m). Athletes were breathing air at 1.8–2 ATA, under the control of a team of physicians. Serum parameters were measured before diving (T0) and: 7 days (T1), 14 days (T2) after the beginning of the dive and 2 h (T3) and 24 h (T4) after resurfacing. Hgb, and many other haematological parameters did not change whereas Ht, s-EPO, the ratio between s-EPO predicted and that observed and reticulocytes (absolute, percent) declined progressively from T0 to T3. At T4 a significant rise in s-EPO was observed. Hgb did not vary but erythropoiesis seemed to be affected as s-EPO and reticulocyte counts showed. All these changes were statistically significant. The experiment, conducted in realistic conditions of dive length, oxygen concentration and pressure, allows us to formulate some hypotheses about the role of prolonged hyperbarism on erythropoiesis. The s-EPO rise, 24 h after resurfacing, is clearly documented and related to the "Normobaric Oxygen Paradox". This evidence suggests interesting hypotheses for new clinical applications such as modulation of s-EPO production and Hgb content triggered by appropriate O_2 administration in pre-surgical patients or in some anemic disease.

CLINICAL APPLICATION : METHODS



Two radomized groups of patients target number n=24
Post cardiac surgery
No hypoxia allowed
No Haemoglobin levels drop

EPO Level in Cardiac Patients post O2 administration (randomely assigned groups)



ion surgeries is clearly needed. Indeed, temperatures from 5°C to 25°C (for example) do not preclude identifying the ole of fluid fluidity variation on clinical IRRSOL absorption while controlling other known variables such as hydrostatic ressure, irrigation flow, and types of surgery and tissue fibroid, endometrium, uterine muscle, prostate, or bladder).

Urological procedures are not only different *per se*, but also ex and age illustrate temperature-related concerns. Young atients may just feel uncomfortably cold, but elderly patients

752

Increase in endogenous erythropoietin synthesis through the normobaric oxygen paradox in cardiac surgery patients

Editor—Exogenous erythropoietins (EPOs) are used worldwide to reduce allogenic blood transfusion exposure. However, their use can be associated with some serious adverse effects[1 2] and has a significant economic impact on public health systems because of the high cost of these drugs.[3]

The normobaric oxygen paradox (NOP) is a new mechanism of triggering endogenous EPO production described in healthy human volunteers.[4] Participants were asked to breathe normobaric oxygen for 2 h at an inspired oxygen fraction (F_{IO_2}) of 100%. After 2 h in the hyperoxic state, participants were quickly switched back to normoxic conditions while breathing air. The authors found that EPO levels were significantly increased during the next 12–36 h compared with baseline levels. This study demonstrated that a sudden and sustained decrease in tissue oxygen tension, without a low level of tissue oxygen tension, could lead to an increase in serum EPO levels in these healthy individuals.[4]

We conducted a prospective, randomized, double-blind pilot trial at one university medical centre to assess the presence of this mechanism among patients undergoing cardiac surgery. After institutional Ethics Committee approval, 20 patients who gave written informed consent were studied. Inclusion criteria were age >18 yr, non-urgent valvular and/or coronary artery bypass graft surgery with the planned use of extracorporeal circulation, and expected postoperative mechanical ventilation in the intensive care unit (ICU). Exclusion criteria were severe preoperative renal disease, severe respiratory disease, and massive intraoperative bleeding. The protocol did not require any modification of the anaesthetic or the surgical routine management of the patient in the operating theatre.

At arrival in the ICU, patients were randomized to two

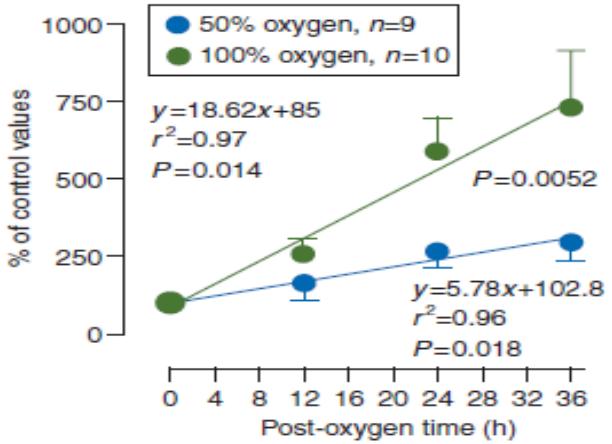


Fig 1 Linear regressions of EPO concentration variations.

cell progenitors, but also on other tissues such as the brain and the heart, where it may exert some protective effects against cellular damage.[5]

Conflict of interest

None declared.

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Medical Hypotheses (2007) xxx, xxx–xxx

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Oxygen breathing may be a cheaper and safer alternative to exogenous erythropoietin (EPO) ☆

R. Burk *

Burk Labs, 9414 168th Place NE, Redmond, WA 98052, USA

Received 22 March 2007; accepted 23 March 2007

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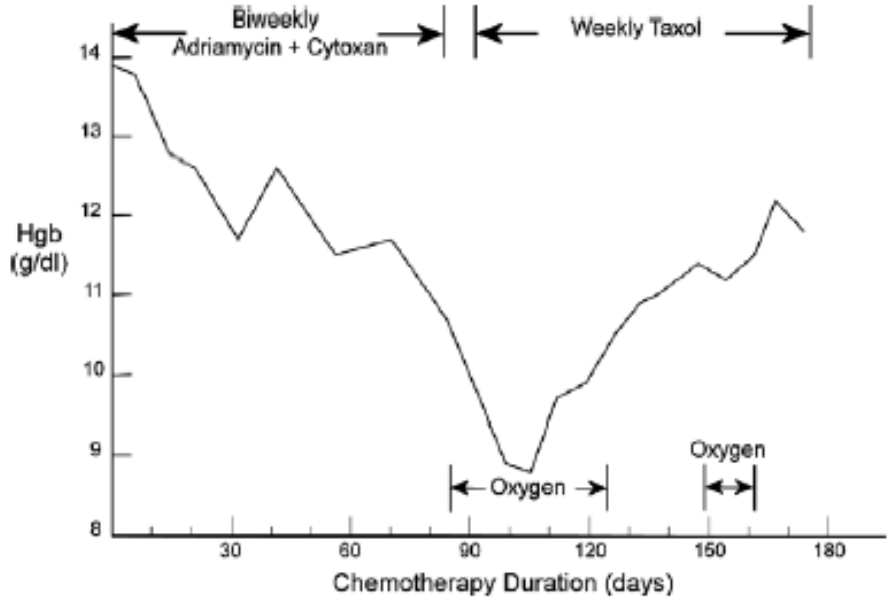
The Balestra study is clear evidence that oxygen breathing can stimulate endogenous EPO, but it is less clear whether this method can effectively treat anemia. A test that lends support to this hypothesis has been performed.

Fig. 1 is the hemoglobin chart of a 42-year old female patient undergoing chemotherapy for stage III breast cancer. The treatment consisted of Adriamycin and Cytoxan, followed by Taxol. As the graph shows, an anemic trend commenced and worsened along with the beginning of chemotherapy treatment.

About 85 days into chemotherapy, treatment with oxygen breathing commenced. This consisted of breathing aviation oxygen (>99% pure oxygen) via a cannula for about 90 min, two to three times



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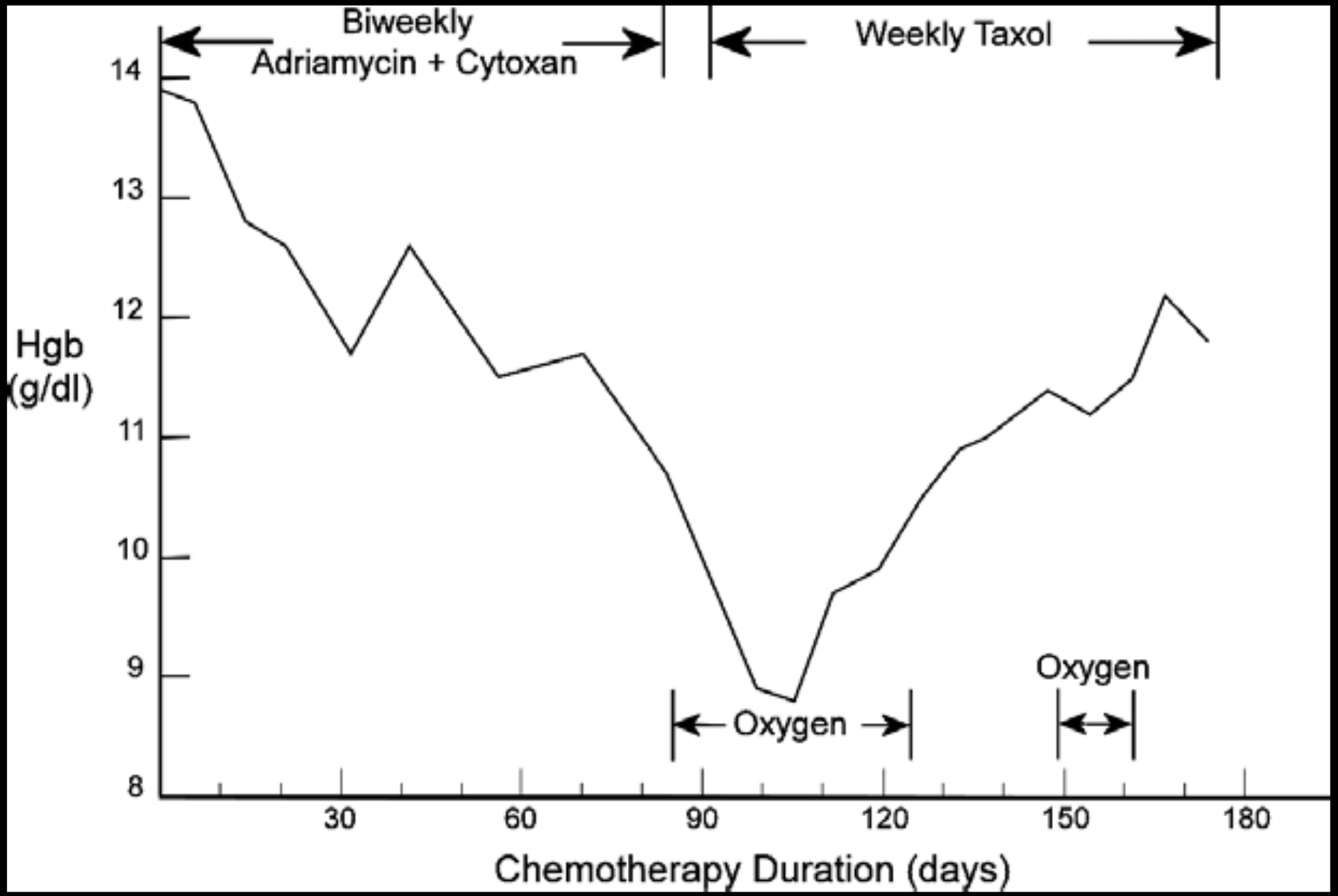
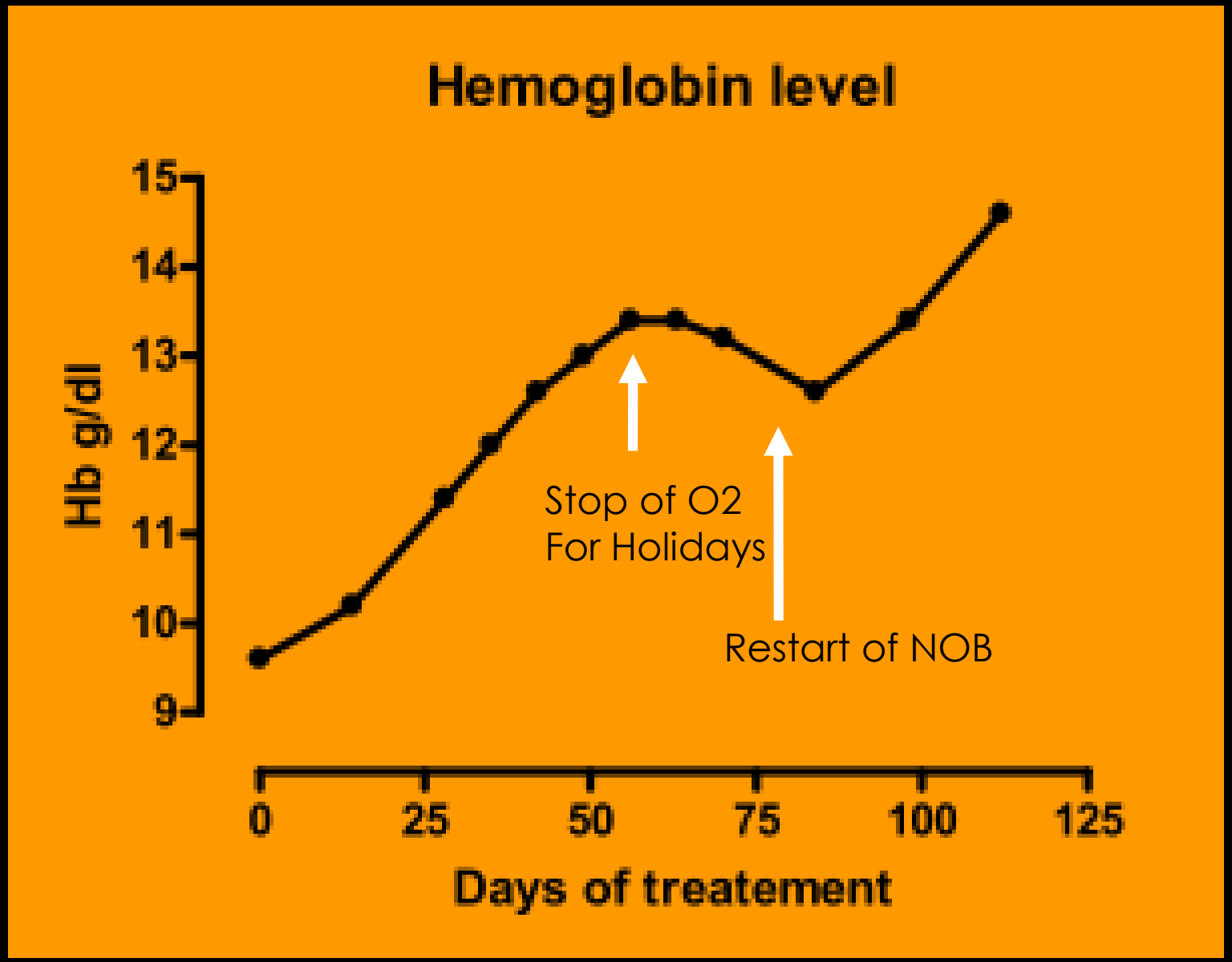
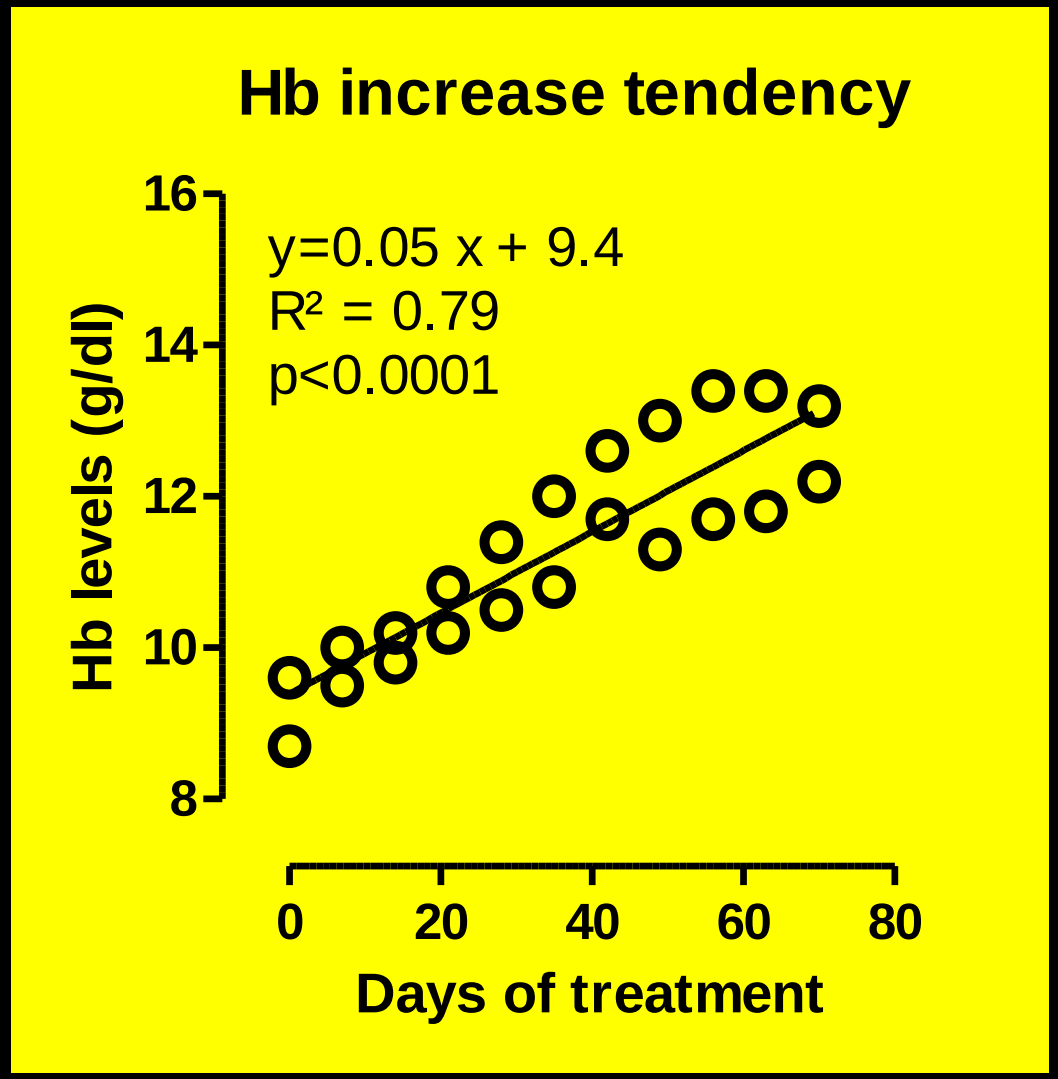

Biweekly
Adriamycin + Cytoxan
Weekly Taxol
Hgb
(g/dl)
14
13
12
11
10
9
8
Oxygen
Oxygen
30
60
90
120
150
180
Chemotherapy Duration (days)


Hemoglobin level
Hb g/dl
15
14
13
12
11
10
9
Stop of O2
For Holidays
Restart of NOB
0
25
50
75
100
125
Days of treatement

PLOTTING THE 2 PATIENTS DATA

Levels of Hb (g/dl) in two patients breathing oxygen. The first 100% O_2 every other day with adjuvant drug therapy (Darbepoetin Alpha + IV iron) (Myelofibrosis), The second breathing 40% O_2 3 times per week with no other erythroid stimulating agents (Chemotherapy).



The 'normobaric oxygen paradox': a simple way to induce endogenous erythropoietin production and concomitantly raise hemoglobin levels in anemic patients

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LETTER TO THE EDITOR

EPO and doping

Costantino Balestra · Peter Germonpré

Accepted: 21 February 2010

To the Editor,

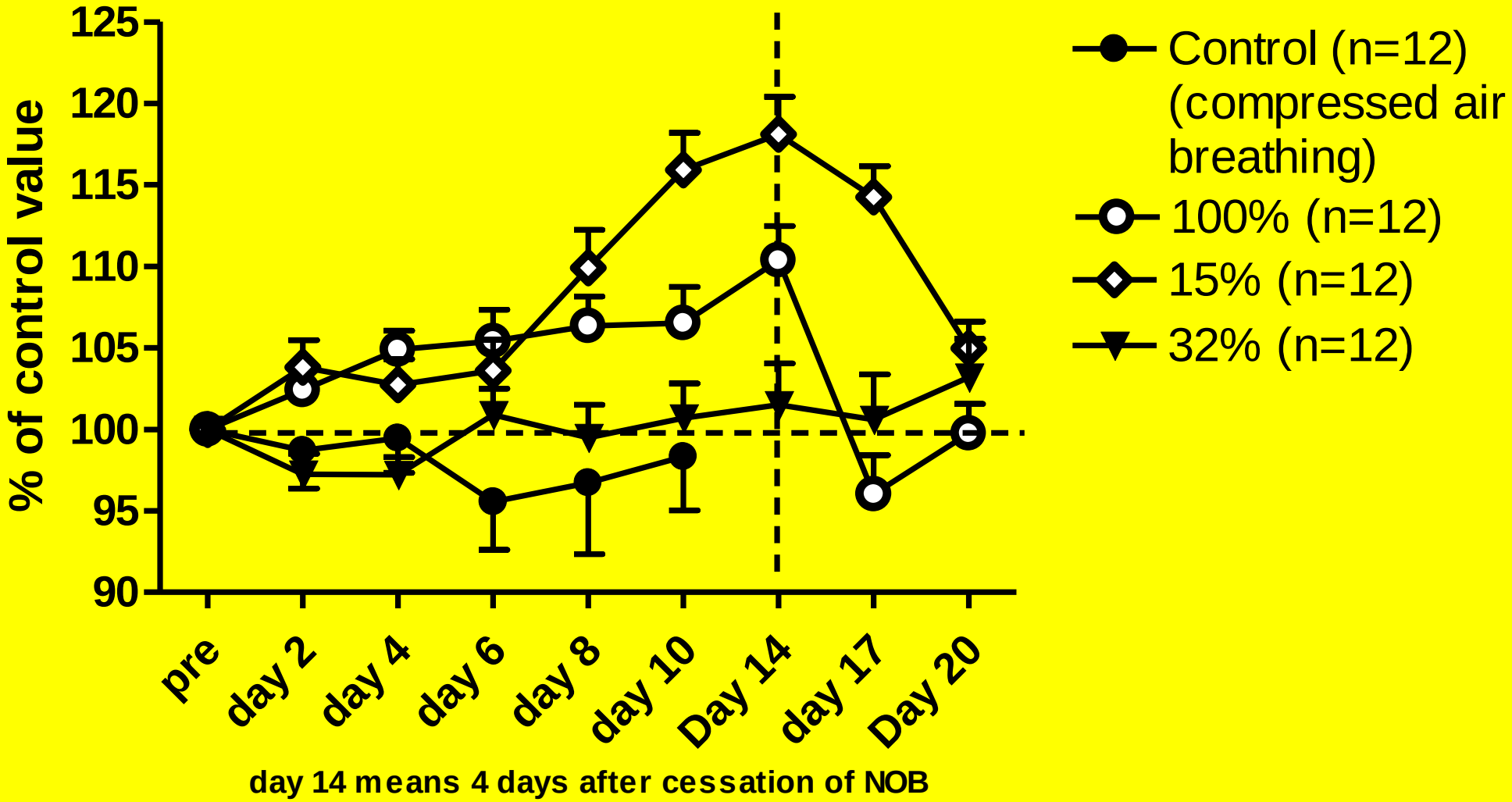
It is with great interest that we read exchanges on intermittent hypoxic (Boning 2009; Ferretti 2009) exposure as a potential doping procedure. Erythropoietin (EPO) does introduce potential concerns in terms of doping, both due to its effects and side effects. An earlier publication on exogenous EPO (Noakes 2008) clearly showed an increase of sub-maximal performance with a significant increase of time to exhaustion after prolonged rHuEPO administration. It is clear that in healthy subjects, at sub-maximal effort levels, cardiac output is sufficient to maintain adequate oxygen delivery to active muscles. Accordingly, it appears that EPO achieves more than increasing blood oxygen carrying capacity alone. Being both a hormone and a cytokine, the actual actions of EPO are complex: EPO is neuroprotective and even neuroregenerative in both the peripheral and central nervous system. Moreover, EPO also has antiapoptotic effects that may be coupled to antioxidant activity.

Exercise-induced plasma volume contraction is linked to

Urine testing for exogenous EPO has been available for several years. It has been used in international cycling events. However, this does not exclude the possibility of endogenous EPO induction. Intermittent hypoxia (Sanchis-Gomar et al. 2009) is the natural trigger for EPO production, and is widely used by (endurance) athletes since many years. We have recently described the use of intermittent hyperoxia to stimulate EPO production (Balestra et al. 2006). This has subsequently been shown to be capable of increasing haemoglobin levels in a chronically anaemic patient (Burk 2007).

The mechanism proposed to explain this "normobaric oxygen paradox" involves a complex play of oxygen-free radicals (OFRs) presence and their "scavenging" enzymes in the cell. In the presence of OFR, the continuously produced hypoxia-inducible factor alpha (HIF-1α) is instantly linked to the (tumour suppressing) Von Hippel Lindau Protein (VHLp). This complex is subsequently ubiquitinized in the prolyl-oxidase pathway and finally recycled in the proteasome. In a hypoxic state, the absence of OFR prevents

Hb Variation after 100% O2 breathing (30 minutes every other day)



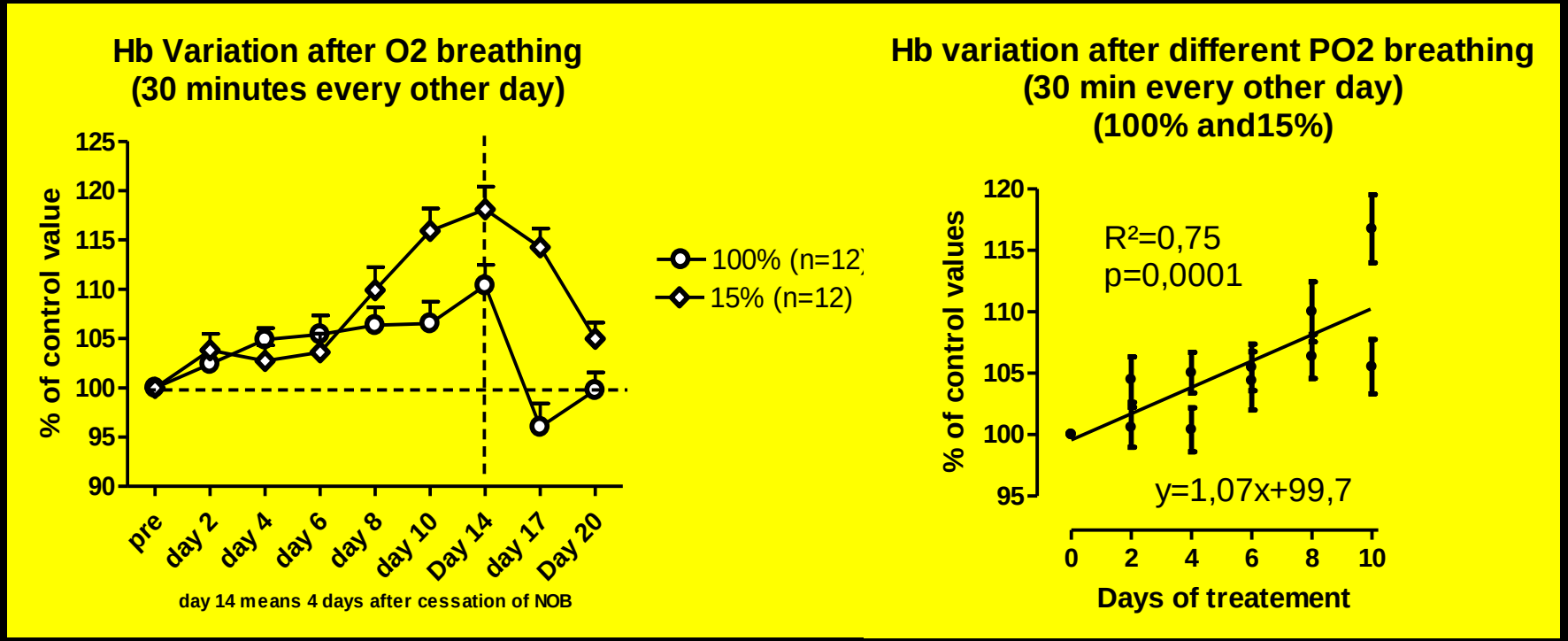
day 14 means 4 days after cessation of NOB

Pulsed high oxygen induces a hypoxic-like response in human umbilical endothelial cells and in humans

F. Cimino, C. Balestra, P. Germonpré, D. De Bels, F. Tillmans, A. Saija, A. Speciale and F. Virgili

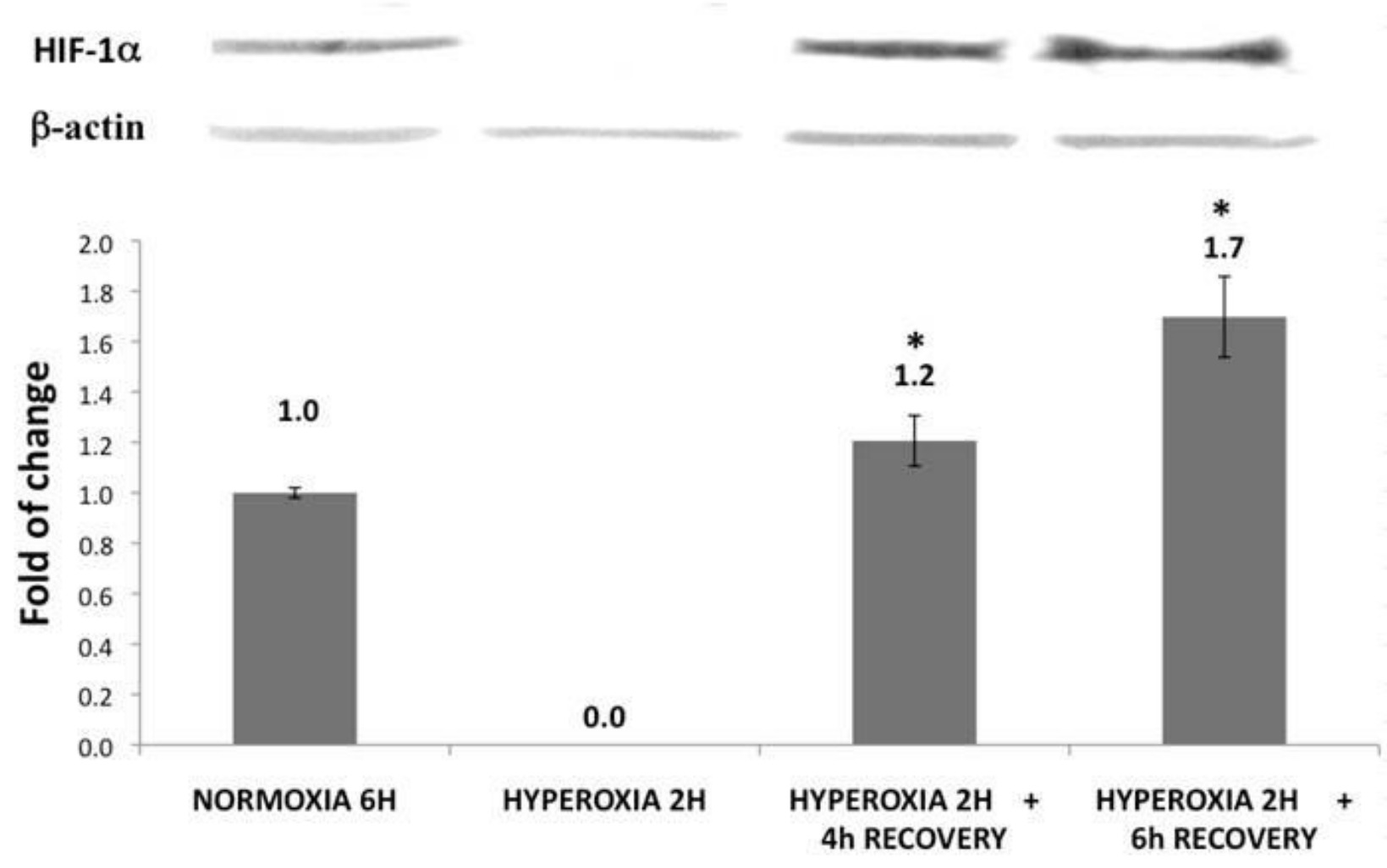
J Appl Physiol 113:1684-1689, 2012. First published 4 October 2012;
doi: 10.1152/japplphysiol.00922.2012

HYPOXIA = HYPEROXIA



HUVEC CELLS

CIMINO F, BALESTRA C, GERMONPRE P, DE BELS D, TILLMANS F, SAIJA A, SPECIALE A & VIRGILI F. (2012). PULSED HIGH OXYGEN INDUCES A HYPOXIC-LIKE RESPONSE IN HUMAN UMBILICAL ENDOTHELIAL CELLS (HUVECS) AND IN HUMANS. *JOURNAL OF APPLIED PHYSIOLOGY*.



INTERMITTENT OXYGEN HYPOXIA-HYPEROXIA

J Appl Physiol 113: 1684–1689, 2012.
First published October 4, 2012; doi:10.1152/japplphysiol.00922.2012.

Pulsed high oxygen induces a hypoxic-like response in human umbilical endothelial cells and in humans

F. Cimino,[1]* C. Balestra,[2]* P. Germonpré,[2,4] D. De Bels,[2,3] F. Tillmans,[2] A. Saija,[1] A. Speciale,[1] and F. Virgili[5]
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Cimino F, Balestra C, Germonpré P, De Bels D, Tillmans F, Saija A, Speciale A, Virgili F. Pulsed high oxygen induces a hypoxic-like response in human umbilical endothelial cells and in humans. *J Appl Physiol* 113: 1684–1689, 2012. First published October 4, 2012; doi:10.1152/japplphysiol.00922.2012.—It has been proposed that relative changes of oxygen availability, rather than steady-state hypoxic or hyperoxic conditions, play an important role in hypoxia-inducible factor (HIF) transcriptional effects. According to this hypothesis describing the "normobaric oxygen paradox", normoxia following a hyperoxic event is sensed by tissues as an oxygen shortage, upregulating HIF-1 activity. With the aim of confirming, at cellular and at functional level, that normoxia following a hyperoxic event is "interpreted" as a hypoxic event, we report a combination of

transfer, angiogenesis, glycolytic metabolism, proliferation, and apoptosis (17).

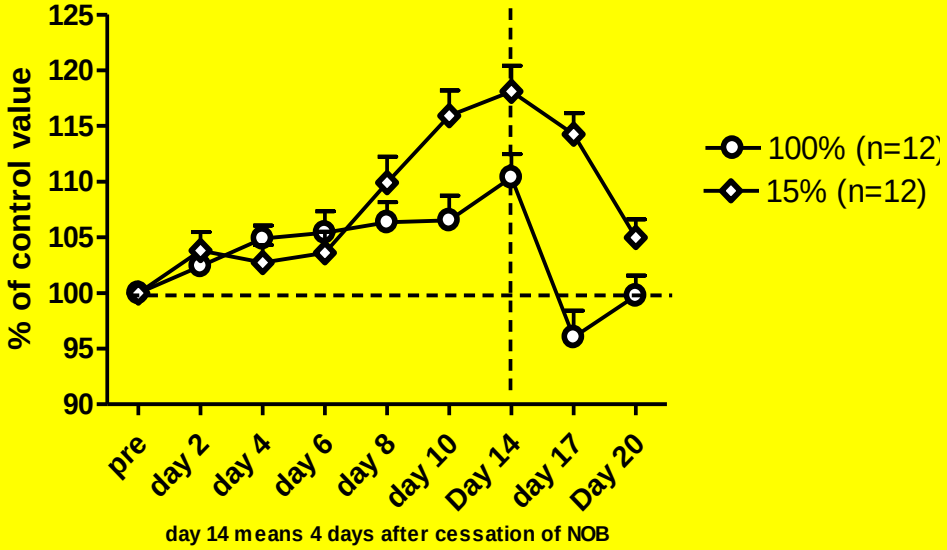
The importance of oxygen concentration sensing by cells in a wide range of cellular responses renders the full understanding of HIF activity an attractive tool to open new avenues in the development of therapeutics able to target HIF pathway, either repressing or activating the expression of a large spectrum of genes in turn involved in a wide spectrum of diseases (29, 30).

According to this pivotal role in metabolism regulation, in the last decade, HIF has been the object of a large number of investigations, which addressed the basis of its mechanism of action. It is established that HIF-1 acts as a heterodimer, consisting of HIF-1α and HIF-1β subunits. HIF-1α represents the regulatory subunit that is primarily activated under conditions of oxygen deprivation, when hydroxylation by prolyl and asparaginyl hydroxylases is inhibited. This results in stabilization and transactivation of HIF-1α, which induces the expression of ~100 target genes by binding to the hypoxia-responsive element (HRE) located in the regulatory DNA sequence (30).

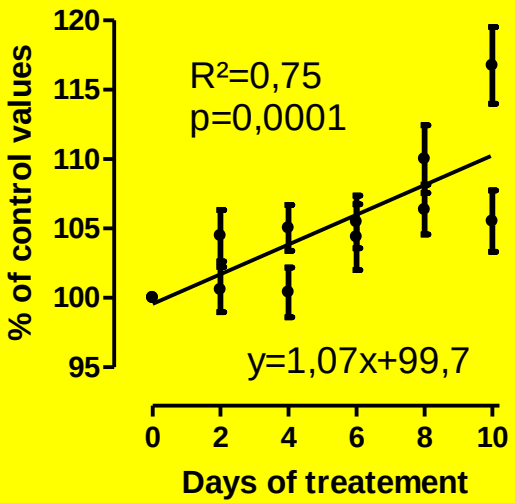
Despite such an established understanding of the basic mechanism of action, some aspects of HIF modulation are still unrevealed. A few years ago, our laboratory proposed a novel mechanism of regulation of HIF activity based on relative changes of oxygen availability rather than on steady-state hypoxic or hyperoxic conditions (5).

On the basis of our experimental observations addressing the effect of rebound relative hypoxia after hyperoxia obtained by normo- and hyperbaric oxygen breathing conditions, we hypothesized that the expression of one of the HIF target genes, erythropoietin (EPO), is modulated by the cellular availability

Hb Variation after O2 breathing (30 minutes every other day)



Hb variation after different PO2 breathing (30 min every other day) (100% and15%)



ORTHOPAEDIC PATIENTS

- Traumatic orthopaedic patients (n=80)
- Followed after surgery for 7 days
- Mean age +/- 80
- Randomized in two groups
  - 1 h/day Oxygen
  - 1 h/day Air
- Blinded, no therapeutic change

	Oxygen Group (n=40)	Air Group (n=40)	P
Sex ratio ♀/♂	32/8 (80% of ♀)	30/10 (75% of ♀)	
Age (Years)	80.4 ± 7.43	81.7 ± 8.41	0.4832
Delay to intervention (Days)	2.03 ± 1.03	2.28 ± 0.96	0.2638
Side ratio (Left/Right)	19/21	22/18	
Type of intervention			
Proximal femoral intramedullar nail	31	28	
Hemiarthroplasty	9	12	
Perioperative blood loss (ml)	473 ± 282	424 ± 378	0.3862
Renal function			
Creatinin	52.6 ± 16.5	47.1 ± 21.7	0.1007
Urea	0.853 ± 0.234	0.763 ± 0.237	0.0556
Glomerular filtration (ml/min)	88.4 ± 22.1	80.3 ± 24.8	0.0512
Associated pathologies			
Hypertension	16	19	
Neurologic diseases	14	14	
Cardiopathy	5	6	
Diabetes	8	7	
COPD	4	5	
Transfusion	3	14	0.0052
No transfusion	37	26	

TRANSFUSION RATE

	Transfusion	No transfusion	Total
Oxygen	3	37	40
Air	14	26	40
Total	17	63	80

p = 0.019, two tailed Fischer's exact test

- 1,2 ± 0,7 RBC/patient Air
- 0,12 ± 0,44 RBC/patient O_2

<0.01

Journal of Clinical Anesthesia (2013) 25, 129–134

Journal of Clinical Anesthesia

Original Contribution

Can the normobaric oxygen paradox (NOP) increase reticulocyte count after traumatic hip surgery?

Pierre Lafère MD (Staff Anesthesiologist)[a,d], Thomas Schubert MD (Staff Surgeon)[b], David De Bels MD (Assistant Professor of Critical Care Medicine)[c,e,*], Peter Germonpré MD (Head, Center for Hyperbaric Oxygen Therapy)[d,e], Costantino Balestra PhD (Head, Environmental and Occupational Physiology Laboratory)[e,f]

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[d]*Center for Hyperbaric Oxygen Therapy, Queen Astrid Military Hospital, 1120 Brussels, Belgium*
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Received 28 November 2011; revised 25 June 2012; accepted 26 June 2012

Keywords:
Allogeneic red blood cell transfusion;
Erythropoietin;
Hip surgeryTraumatic;
Normobaric oxygen paradox;
Reticulocytes;
Transfusion;

Abstract

Study Objective: To determine if the normobaric oxygen paradox (NOP) was effective in increasing reticulocyte count and reducing postoperative requirements for allogeneic red blood cell transfusion after traumatic hip surgery.

Design: Prospective, randomized, double blinded, multi-center study.

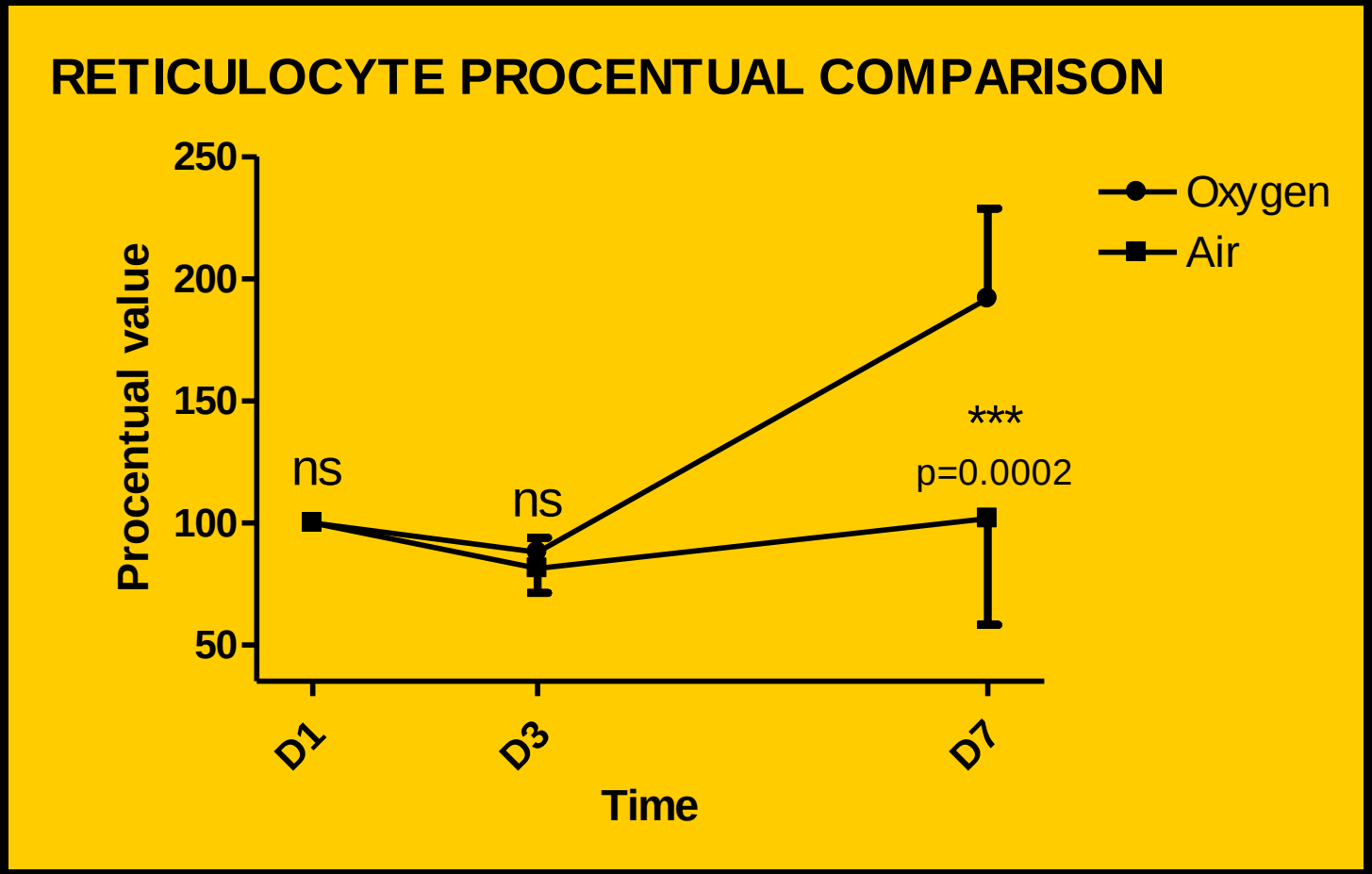
Setting: Surgical wards of two academic hospitals.

Patients: 85 ASA physical status 1 and 2 patients undergoing surgery for traumatic hip fracture.

Interventions: Patients were randomly assigned to receive 30 minutes of air [air group (control); n = 40] or 30 minutes of 100% oxygen (O_2 group; n = 14) at 15 L/min every day from the first postoperative day (POD 1) until discharge.

Measurements: Venous blood samples were taken at admission and after surgery on POD 1, POD 3, and POD 7. Hemoglobin (Hb), hematocrit (Hct), reticulocytes, hemodynamic variables, and transfusion requirements were recorded, as were hospital length of stay (LOS) and mortality.

Main Results: Full analysis was obtained for 80 patients. On hospital discharge, the mean increase in reticulocyte count was significantly higher in the O_2 group than the air group. Percent variation also increased: 184.9% ± 41.4% vs 104.7% ± 32.6%, respectively; $P < 0.001$. No difference in Hb or Hct levels was noted at discharge. Allogeneic red blood cell transfusion was 7.5% in the O_2 group versus 35% in the air group ($P = 0.0052$). Hospital LOS was significantly shorter in the O_2 group than the air group (7.2 ± 0.7 days vs 7.8 ± 1.6 days, respectively; $P < 0.05$).



Both Surgeons received Congratulations From the Blood bank one year after the Experiment…….Guess Why??

Hyperoxia may be beneficial

Enrico Calzia, MD, PhD; Pierre Asfar, MD, PhD; Balász Hauser, MD, PhD; Martin Matejovic, MD, PhD; Costantino Ballestra, PhD; Peter Radermacher, MD, PhD; Michael Georgieff, MD, PhD

The current practice of mechanical ventilation comprises the use of the least inspiratory O_2 fraction associated with an arterial O_2 tension of 55 to 80 mm Hg or an arterial hemoglobin O_2 saturation of 88% to 95%. Early goal-directed therapy for septic shock, however, attempts to balance O_2 delivery and demand by optimizing cardiac function and hemoglobin concentration, without making use of hyperoxia. Clearly, it has been well-established for more than a century that long-term exposure to pure O_2 results in pulmonary and, under hyperbaric conditions, central nervous O_2 toxicity. Nevertheless, several arguments support the use of ventilation with 100% O_2 as a supportive measure during the first 12 to 24 hrs of septic shock. In contrast to patients without lung disease undergoing anesthesia, ventilation with 100% O_2 does not worsen intrapulmonary shunt under conditions of hyperinflammation, particularly when low tidal volume–high positive end-expiratory pressure ventilation is used. In healthy volunteers and experimental animals, exposure to hyperoxia may cause pulmonary inflammation, enhanced oxidative stress, and tissue apoptosis. This, however, requires long-term exposure or injurious tidal volumes. In contrast, within the timeframe of a perioperative administration, direct O_2 toxicity only plays a negligible role. Pure O_2 ventilation induces peripheral vasoconstriction and thus may counteract shock-induced hypotension and reduce vasopressor requirements. Furthermore, in experimental animals, a redistribution of cardiac output toward the kidney and the hepato-splanchnic organs was observed. Hyperoxia not only reverses the anesthesia-related impairment of the host defense but also is an antibiotic. In fact, perioperative hyperoxia significantly reduced wound infections, and this effect was directly related to the tissue O_2 tension. Therefore, we advocate mechanical ventilation with 100% O_2 during the first 12 to 24 hrs of septic shock. However, controlled clinical trials are mandatory to test the safety and efficacy of this approach. (Crit Care Med 2010; 38[Suppl.]:S559–S568)

Key Words: early goal-directed therapy; septic shock; vasoconstrictor; intrapulmonary shunt; hypoxic pulmonary vasoconstriction; oxygen radicals; oxidative stress; oxygen toxicity; nitric oxide; apoptosis; leukocyte endothelial interaction; normobaric oxygen paradox; erythropoietin

Original articles

The 'normobaric oxygen paradox': does it increase haemoglobin?

David De Bels, Sigrid Theunissen, Jacques Devriendt, Peter Germonpré, Pierre Lafere, Joseph Valsamis, Thyl Snoeck, Philippe Meeus and Costantino Balestra

Abstract

(De Bels D, Theunissen S, Devriendt J, Germonpré P, Lafere P, Valsamis J, Snoeck T, Meeus P, Balestra C. The 'normobaric oxygen paradox': does it increase haemoglobin? *Diving and Hyperbaric Medicine*. 2012;42(2):67-71.)

Background: A novel approach to increasing erythropoietin (EPO) using oxygen (O_2) (the 'normobaric oxygen paradox') has been reported in healthy volunteers. We investigated whether the EPO increase is sufficient to induce erythropoiesis by comparing two protocols of O_2 administration.

Methods: We compared the effect of daily versus alternate days 100% O_2, breathed for 30 minutes, on haemoglobin concentrations during a 12-day period. Nine subjects underwent the two protocols six weeks apart.

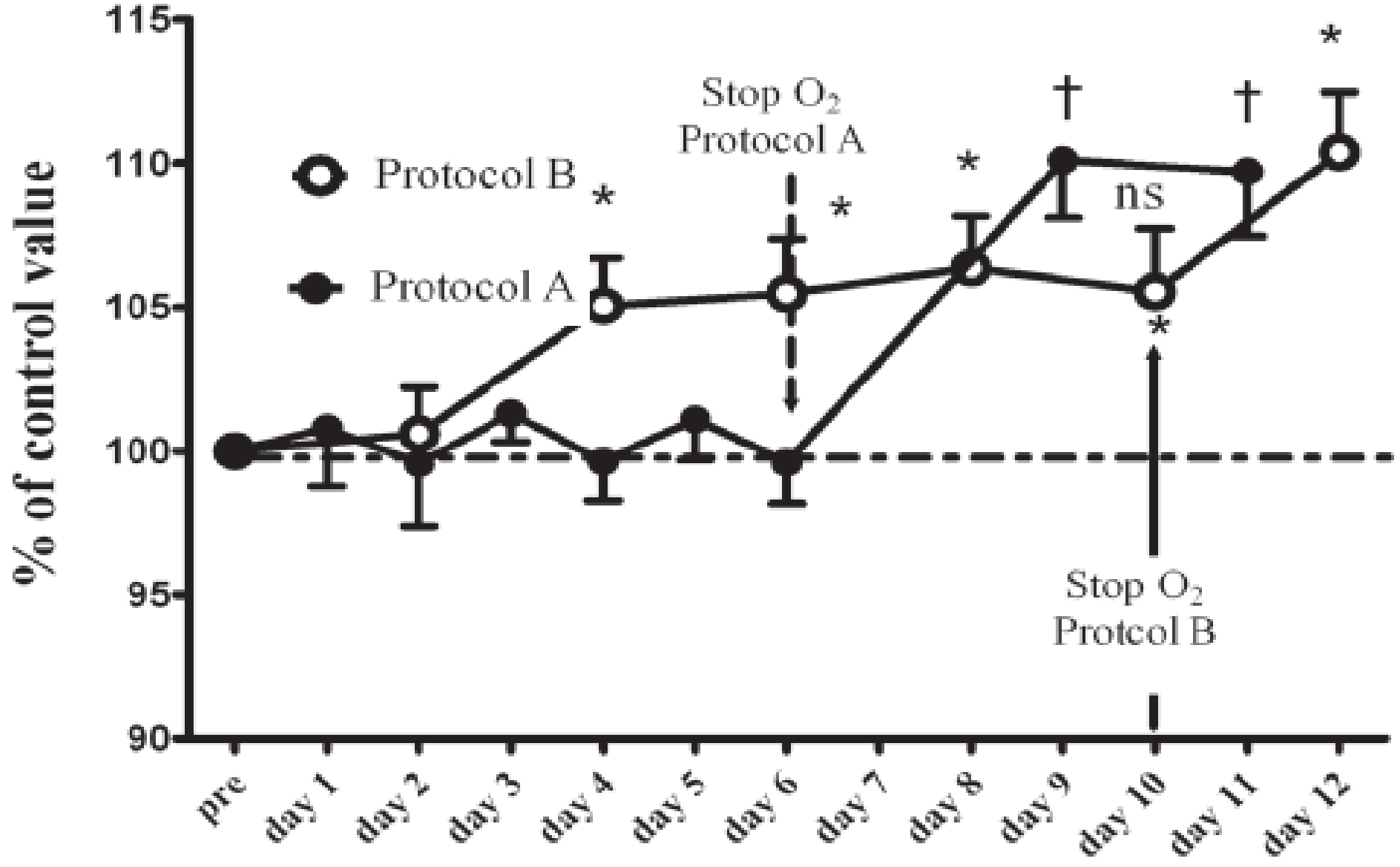
Results: We observed a significant increase in haemoglobin (as a percentage of baseline) in the alternate-days group compared to the daily group and to baseline after four days (105.5 ± 5.7 % vs. 99.6 ± 3.3 % difference from baseline; $P < 0.01$). At the end of the experimental period, haemoglobin values increased significantly compared to baseline in both groups. There was a significant percentage rise in reticulocyte count in the alternate-days group compared to the daily group (182 ± 94 % vs. 93 ± 34 %; $P < 0.001$).

Conclusion: The normobaric oxygen paradox seems effective in increasing haemoglobin in non-anaemic, healthy volunteers, providing sufficient time is allowed between O_2 applications. The exact time interval is not clearly defined by this study but should probably be at least or greater than two days. Further studies are needed to define more precisely clinical applications in the use of O_2 as a pharmaceutical agent.

Key words

Oxygen, haematology, reactive oxygen species (ROS), physiology

Comparison baseline haemoglobin after 30 minutes of 100% O_2 breathing daily (protocol A; † $P < 0.01$) or on alternate days (protocol B; * $P < 0.01$); ns – not significant



Oxygen Sensing, Homeostasis, and Disease

TO THE EDITOR: Two points could have been added to the review article by Semenza (Aug. 11 issue)[1] on a fundamental mechanism in cell, tissue, and organ metabolism. First, considering the metabolic signals modifying signal transduction, the author mentions hypoxia as the sole trigger to expression of hypoxia-inducible factor 1 (HIF-1). One study[2] pointed out the possible role of nonhypoxic partial pressure of oxygen (PO_2) variation as a trigger to HIF-1α. In this model, transient normobaric hyperoxia followed by a return to normoxia led to a significant increase in serum erythropoietin concentration. This increase began 8 hours after the return to normoxia, which is consistent with the time frame of gene expression.

Second, in the section on co-opted adaptation to hypoxia in cancer, the author points out that intratumoral hypoxia is associated with increased risks of metastasis and death. This finding has been the trigger for research on the consequences of hyperoxia on cancer-cell survival. A recent hypothesis[3] is that transient normobaric hyperoxia could be deleterious for tumor cells and, in parallel, beneficial (cytoprotective) for normal cells; this could open interesting therapeutic options in adjuvant treatments against cancer.

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No potential conflict of interest relevant to this letter was reported.

1. Semenza GL. Oxygen sensing, homeostasis, and disease. N Engl J Med 2011;365:537-47. [Erratum, N Engl J Med 2011; 365:968.]
2. Balestra C, Germonpré R, Poortmans JR, Marroni A. Serum erythropoietin levels in healthy humans after a short period of normobaric and hyperbaric oxygen breathing: the "normobaric oxygen paradox." J Appl Physiol 2006;100:512-8.
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TO THE EDITOR: The review by Semenza examines the role of HIF-1α in the context of hypoxia and ischemia. However, we think that the role of HIF-1α can be seen from another point of view. HIF-1α does not appear to be the clear hypoxic marker.[1] It is stabilized not only because of hypoxia but also by metabolic imbalances, induced growth, and lower intracellular pH values. The curious association of metabolic pathways and different metabolites[2] with this marker causes doubt about the function of HIF-1 as a molecular regulator to oxygen deprivation. The fact that hypoxia always decreases the intracellular pH value[3] discloses another face of HIF-1 beyond the phenomenon called hypoxia. The biologic function of this protein is rather that of a sensitive controller and regulator of an adaptive metabolic response to alterations of the pH value. That this function is independent from the oxygen status of cells is reflected by a multitude of HIF-1 detections at normoxia.[4] Altogether, we suggest that HIF-1 is mainly a sensor and regulator for the intracellular pH value.

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EXPERT OPINION

The "Normobaric Oxygen Paradox": a new tool for the anesthetist?

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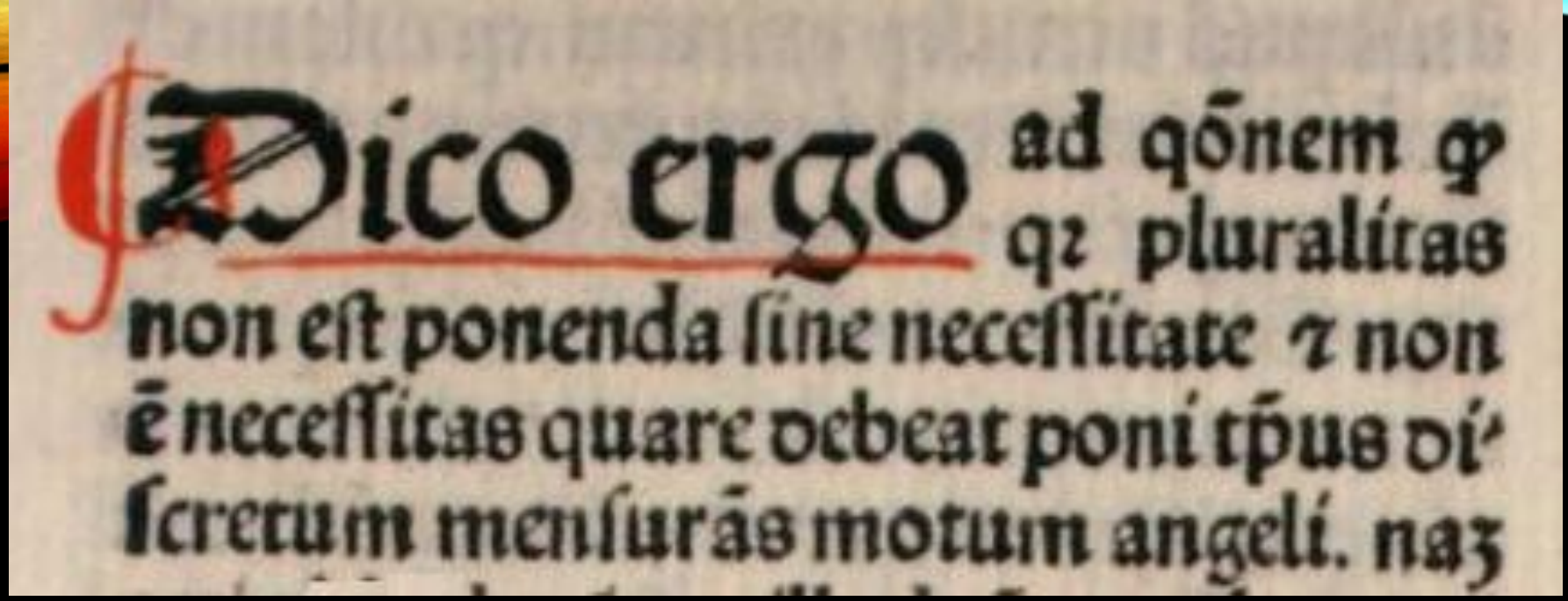
ABSTRACT

Hypoxia is the natural trigger for endogenous EPO production but recently the use of intermittent hyperoxia to stimulate EPO has been postulated and this phenomenon has been called the "normobaric oxygen paradox" (NOP). The "NOP" is a mechanism by which oxygen regulates the expression of the Hypoxia Inducible Factor 1 alpha (HIF-1α). The HIF-1α-depending gene regulation is responsible for many different genetic expressions including EPO and VEGF. It has been proposed that relative changes of oxygen availability rather than steady state hypoxic or hyperoxic conditions, play an important role in HIF transcriptional effects. According to this hypothesis, the cell interprets the return to normoxia after a hyperoxic event as an oxygen shortage, and induces HIF-1-regulated gene synthesis, including EPO. Being both a hormone and a cytokine, the actual actions of EPO are complex: its clinical utility has been postulated for neuroprotection and cardioprotection. The precise level of inspired oxygen and the exact time-frame for its iterative administration are not totally known. N-Acetyl-L-Cysteine (NAC) supplementation has been shown to help. All the reported data demonstrate how hyperoxic and hypoxic states can potentially be manipulated if oxygen is been considered as a multifaceted molecule more than just a gas.

(Minerva Anestesiol 2014;80:366-72)

Key words: Oxygen - Hyperoxia - Erythropoietin.

NAC - I - O_2



« Pluralitas non est ponenda sine necessitate »

Occham's Razor

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The normobaric oxygen paradox: A novel way to administer oxygen as an adjuvant treatment for cancer?

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ABSTRACT

The "normobaric oxygen paradox" is a dual mechanism by which oxygen regulates the expression of the Hypoxia Inducible Factor 1 alpha (HIF-1α). The HIF-1α-depending gene regulation is responsible for many different genetic expressions including EPO and VEGF that are usually expressed in parallel.

First, VEGF under-expression could decrease tumor angiogenesis leading to a decrease in tumor growth or even apoptosis of cancer cells.

Second, induction of EPO-expression can provide cytoprotection.

Altogether, this could be deleterious for cancer cells while helping non-malignant cells (at least neural and cardiac) cells to be protected from the side effects of chemotherapy. Eventually, HIF induction could boost immune response by inflammatory cells, increasing their antitumor activity.

Introduction

Cancer still remains one of the leading causes of death worldwide. The therapeutic arsenal is regularly increasing and most chemotherapeutic agents aim at inducing selective apoptosis of cancer cells. A deficit in the apoptotic machinery can be seen in more than 50% of cancers [1]. The "normobaric oxygen paradox" seems to have a beneficial effect on chemotherapy-induced anemia [2,3] while inducing modifications in the cellular mechanisms of adaptation to hypoxia.

Hypothesis

hypoxia. This latter depends on oxygen free radicals availability. In fact, in presence of reactive oxygen species (ROS) and under normoxic conditions, the hypoxia Inducible Factor 1 alpha, (HIF-1α) is hydroxylated by prolyl-hydroxylase. This results in ubiquitylation by the Von Hippel Lindau tumor suppressing Protein (VHLp) and finally in the degradation of HIF-1α in the proteasome (see Fig. 1). In case of limited availability or absence of reactive oxygen species, the HIF-1α will not link with VHLp and thus can be dimerized with the HIF-1β. This HIF complex can thus bind to target promoters known as hypoxia responsive elements leading to the transcription of the erythropoietin gene as well as many other genes involved in cellular metabolism [5].

BMC Cancer

BioMed Central

Research article

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Hyperoxia retards growth and induces apoptosis and loss of glands and blood vessels in DMBA-induced rat mammary tumors

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RAA A, STANSBERG C, STEEN VM, BJERKVIG R, REED RK & STUHR LE. (2007). HYPEROXIA RETARDS GROWTH AND INDUCES APOPTOSIS AND LOSS OF GLANDS AND BLOOD VESSELS IN DMBA-INDUCED RAT MAMMARY TUMORS. *BMC CANCER* **7,** 23.

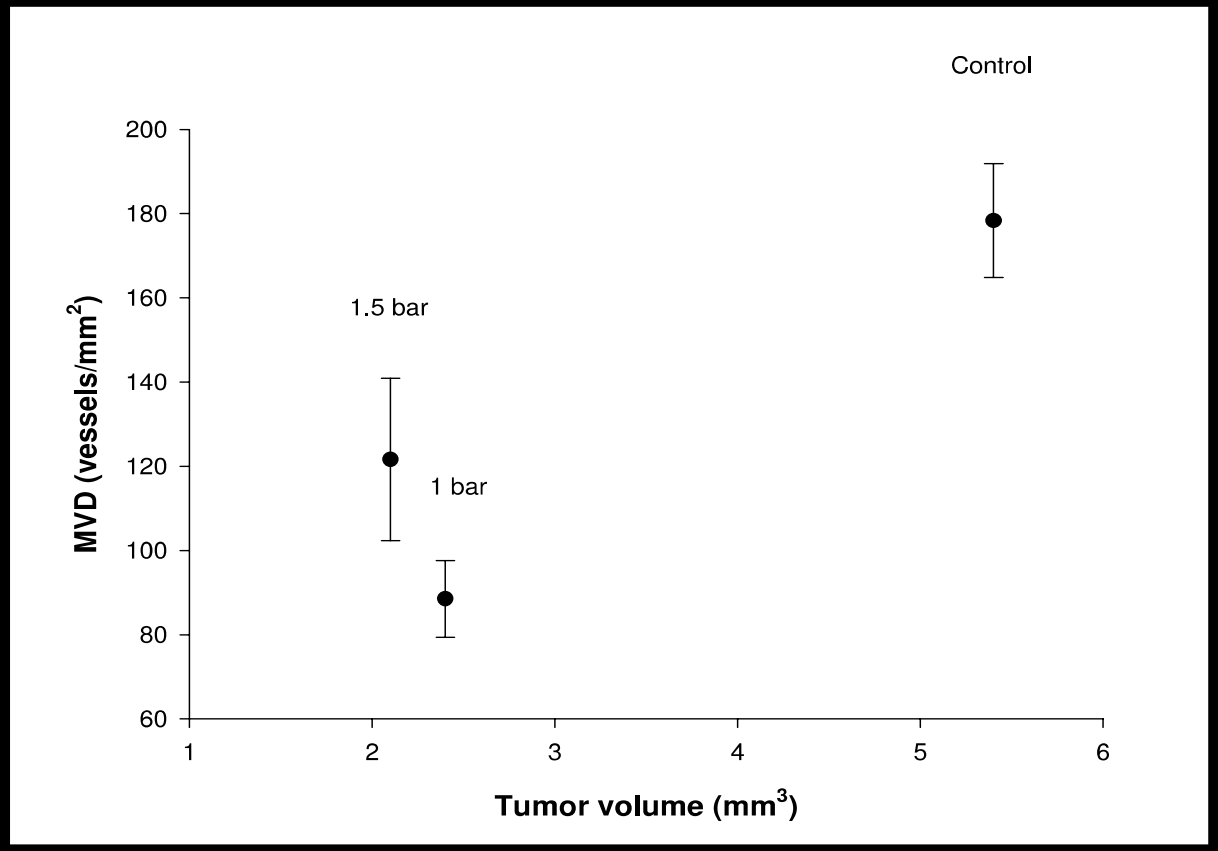


Figure 2. Relationship between tumor size and blood vessels per

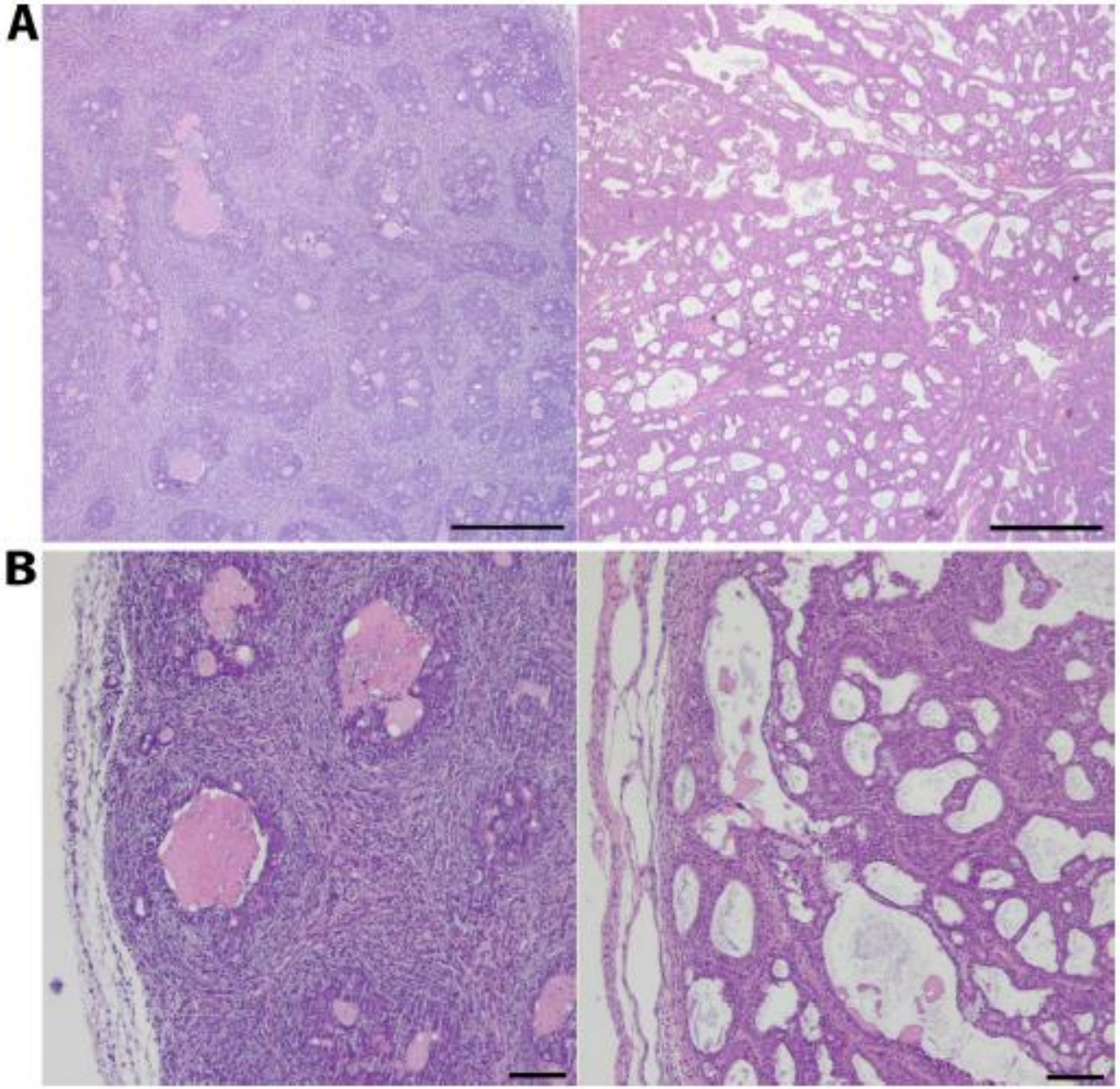
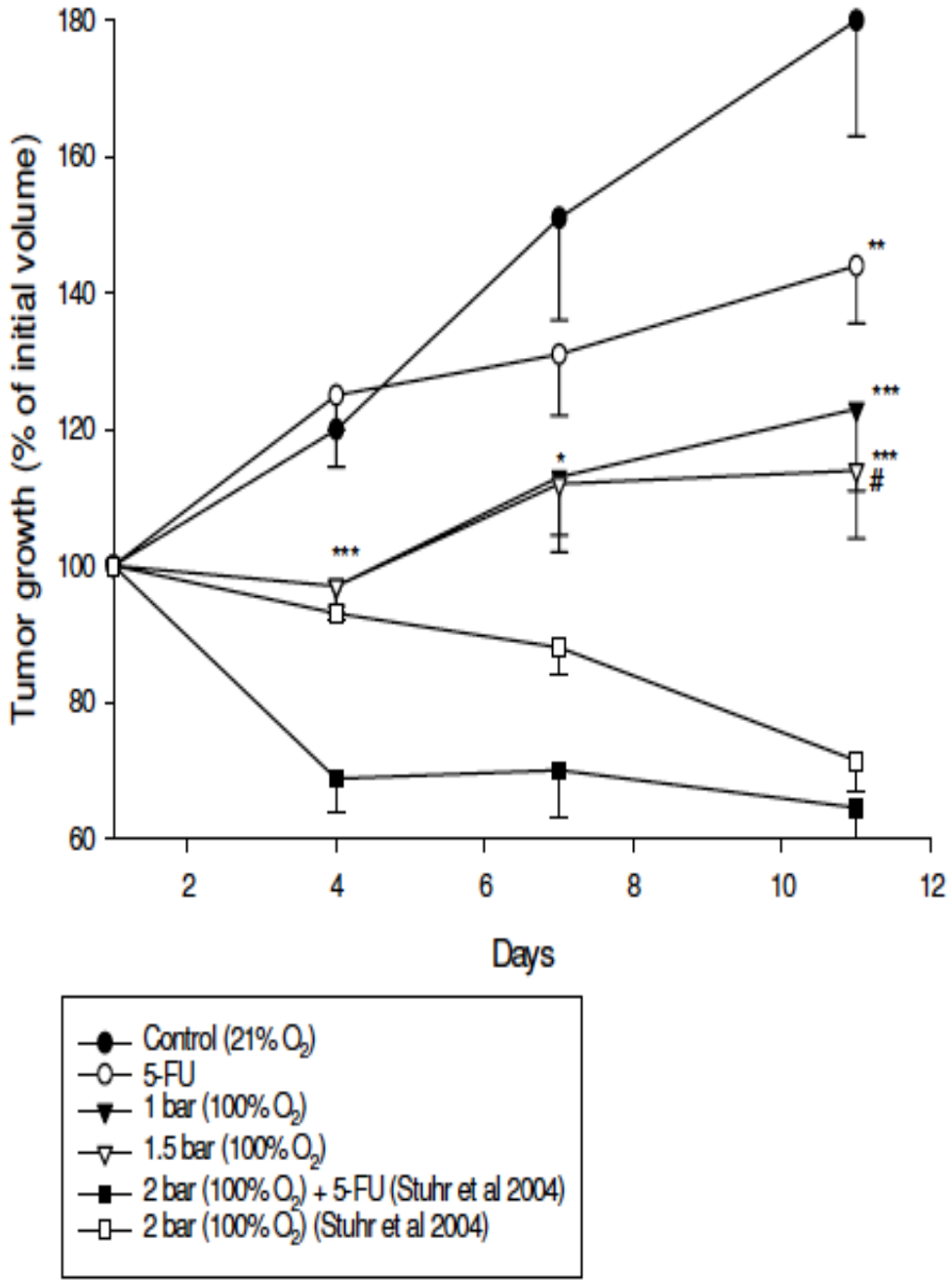
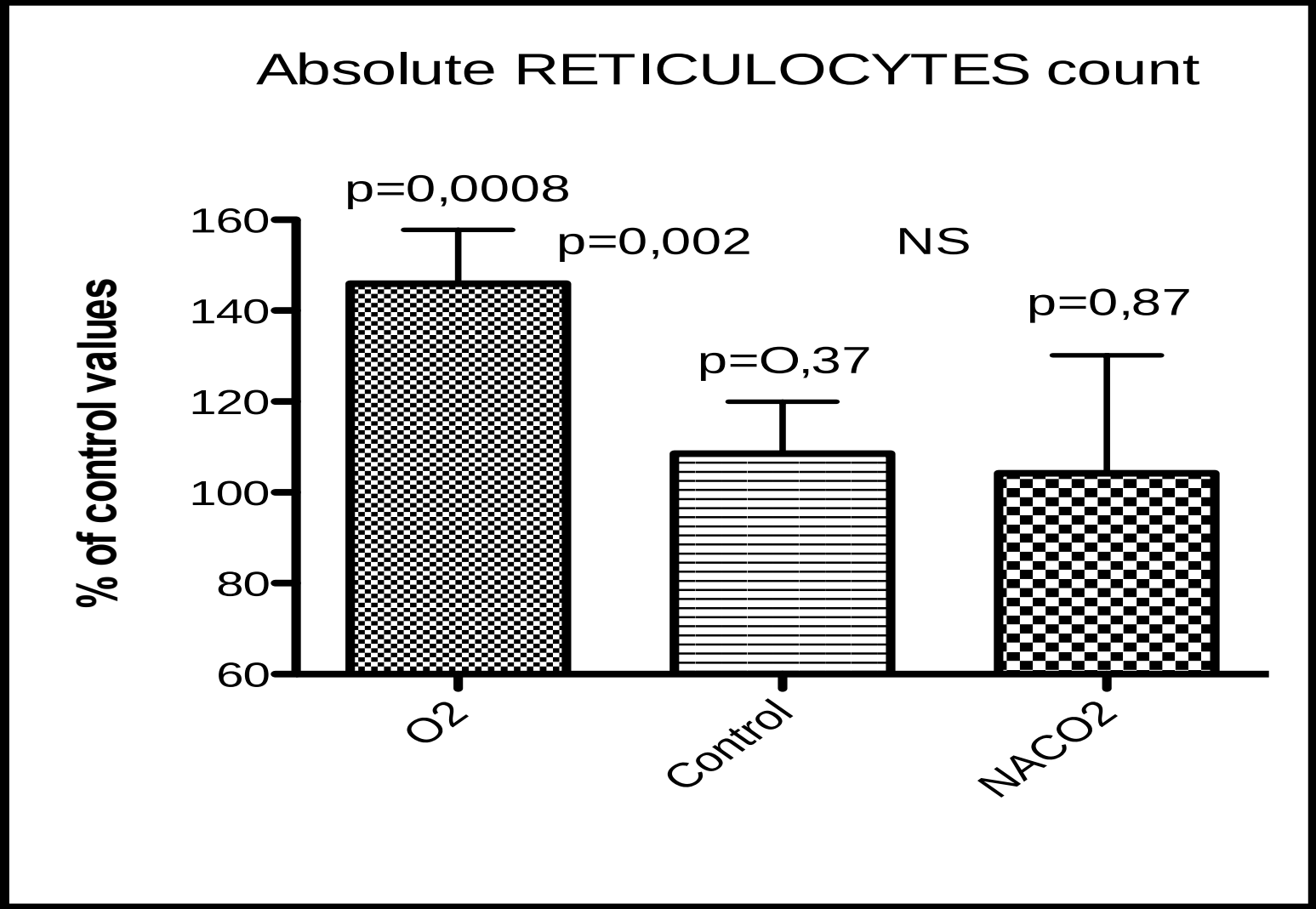


Figure 2
Examples of eosin-hematoxylin stained tumor-tissue of the central (A) and peripheral (B) part of the mammary tumor in control (left) and during hyperoxic treatment (right, 1 bar, pO_2 = 1.0). The images under A are scaled to the same magnification (× 4) and the images under B to the same magnification (× 10). Scale bar indicate 500 μm (A) and 100 μm (B).



ABDOMINAL ONCOLOGIC PATIENTS N=60



FRACTAL DIMENSION OF LEUKEMIC CELLS AFTER HYPEROXIA

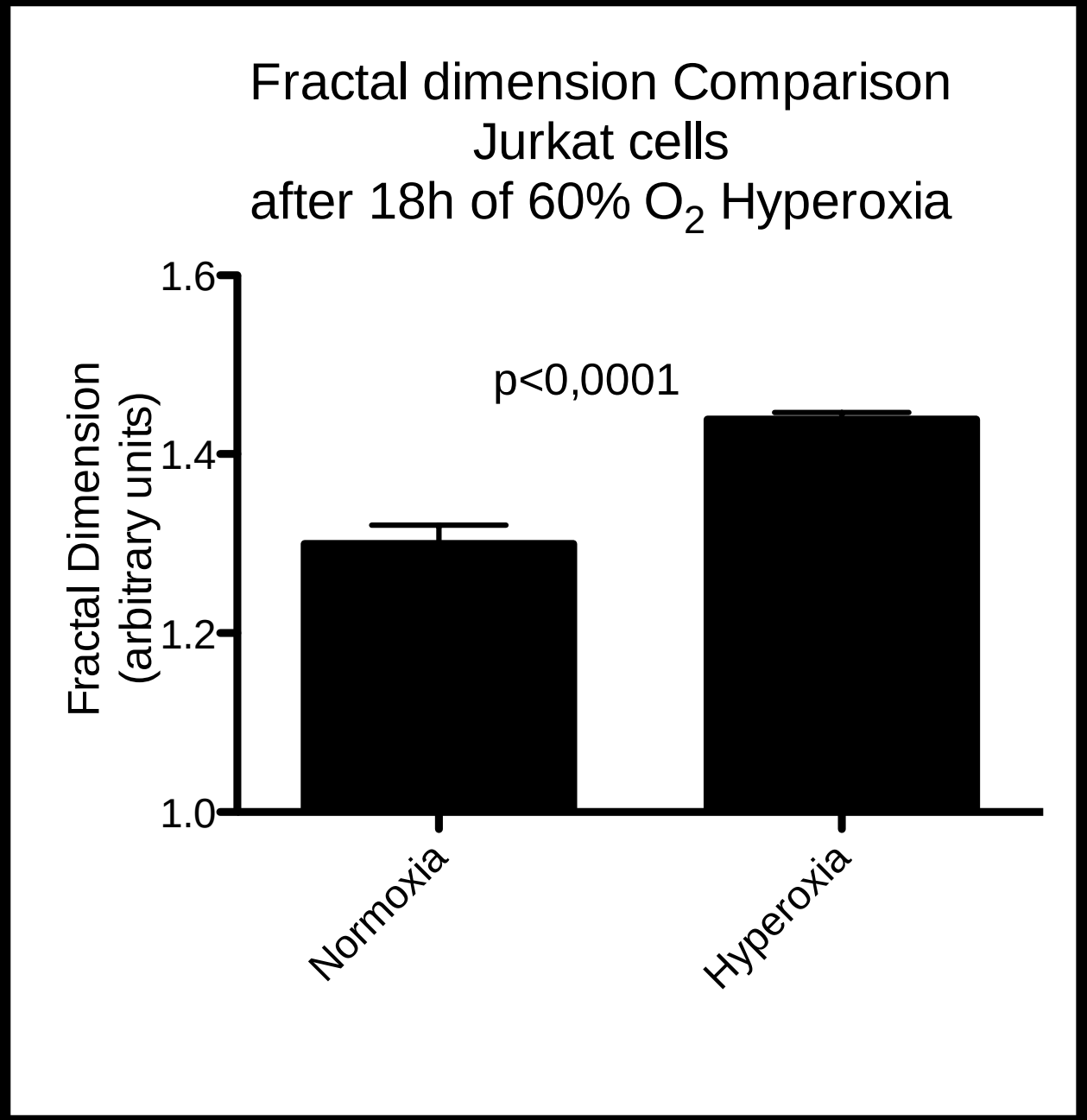
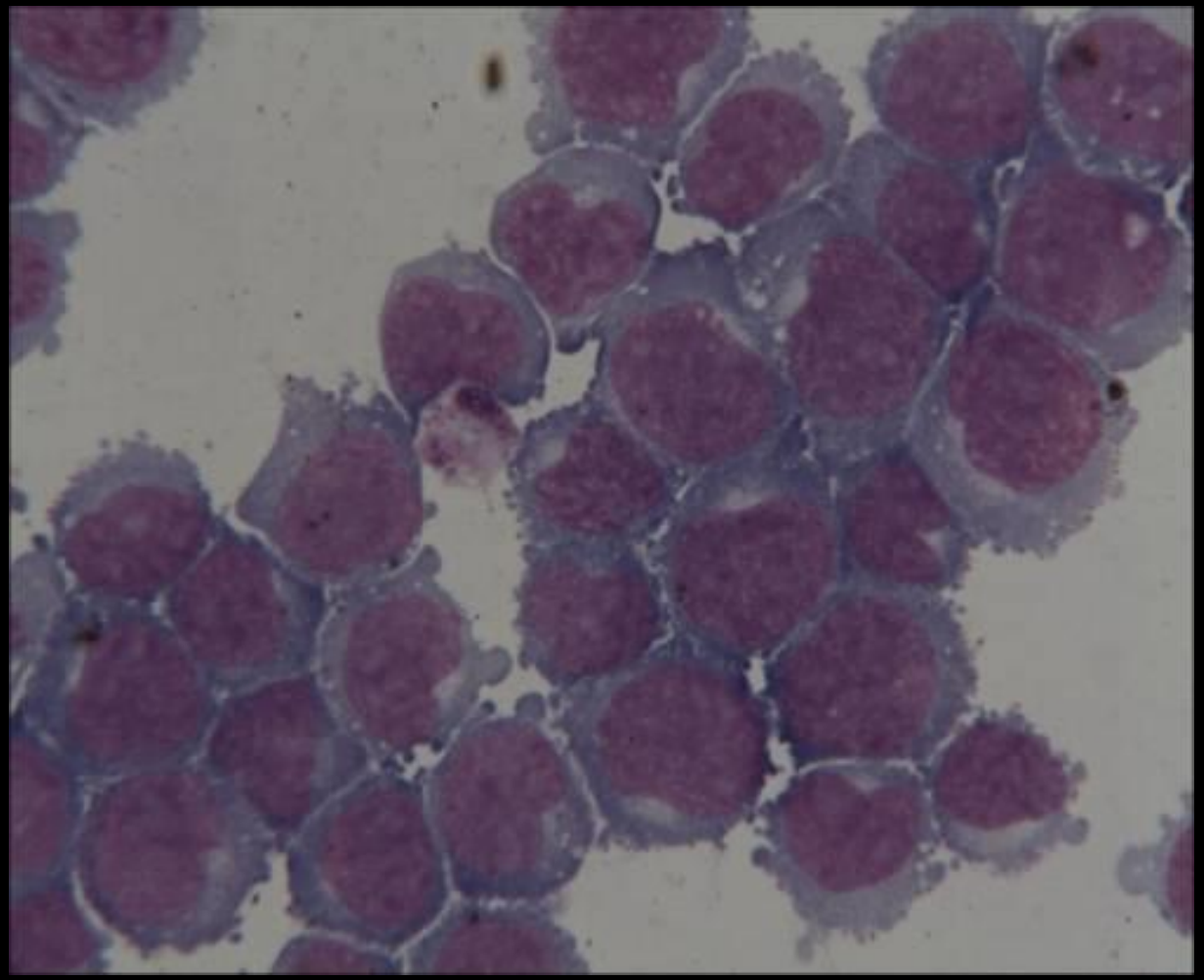
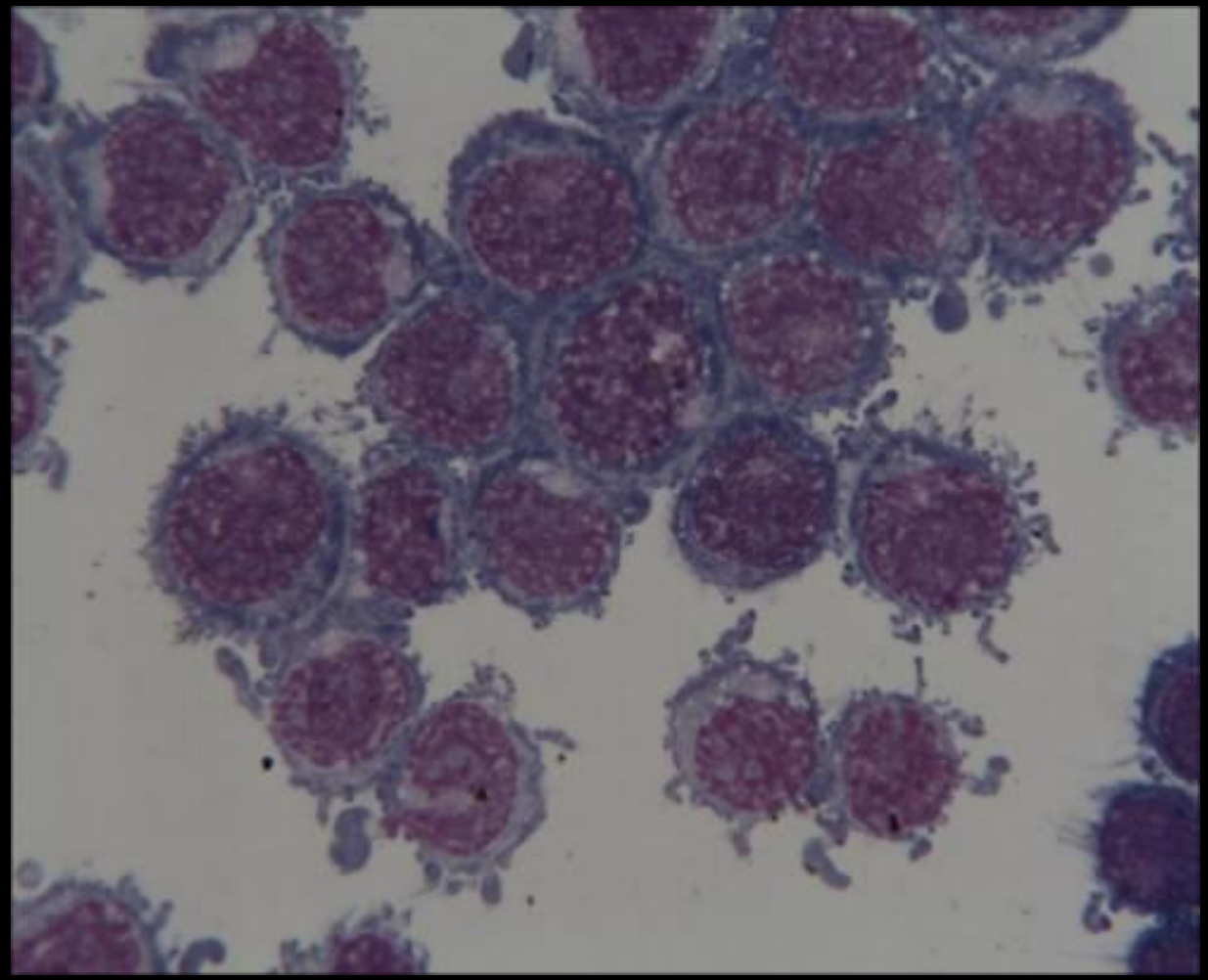
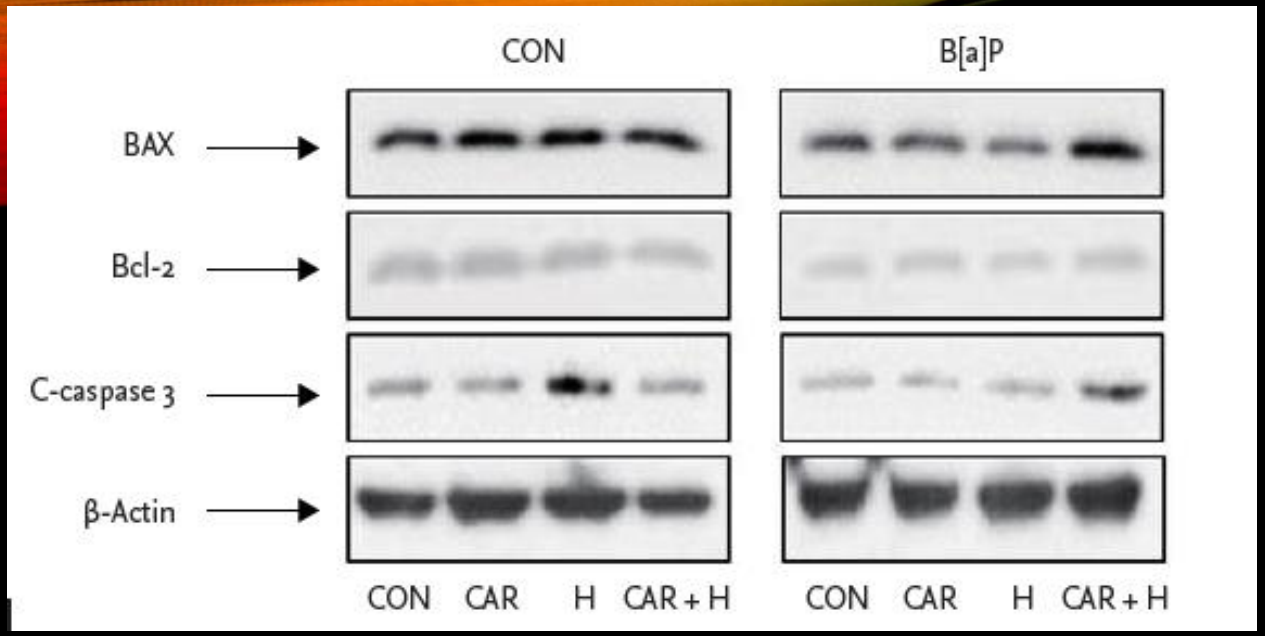


Figure 4





50x



KEY MESSAGE

1. Intermittent normobaric hyperoxia with carboplatin displays a synergistic tumoricidal effect in a mouse lung cancer model.
2. Addition of hyperoxia to chemotherapy enhanced oxidative stress, which is considered to induce cell death mainly via apoptosis.
3. Intermittent normobaric hyperoxia may be a useful adjuvant therapy for lung cancer.

ORIGINAL ARTICLE

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KJIM

Combination of carboplatin and intermittent normobaric hyperoxia synergistically suppresses benzo[a]pyrene-induced lung cancer

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Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, The Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background/Aims: We explored the effects of intermittent normobaric hyperoxia alone or combined with chemotherapy on the growth, general morphology, oxidative stress, and apoptosis of benzo[a]pyrene (B[a]P)-induced lung tumors in mice.

Methods: Female A/J mice were given a single dose of B[a]P and randomized into four groups: control, carboplatin (50 mg/kg intraperitoneally), hyperoxia (95% fraction of inspired oxygen), and carboplatin and hyperoxia. Normobaric hyperoxia (95%) was applied for 3 hours each day from weeks 21 to 28. Tumor load was determined as the average total tumor numbers and volumes. Several markers of oxidative stress and apoptosis were evaluated.

Results: Intermittent normobaric hyperoxia combined with chemotherapy reduced the tumor number by 59% and the load by 72% compared with the control B[a]P group. Intermittent normobaric hyperoxia, either alone or combined with chemotherapy, decreased the levels of superoxide dismutase and glutathione and increased the levels of catalase and 8-hydroxydeoxyguanosine. The Bax/Bcl-2 mRNA ratio, caspase 3 level, and number of transferase-mediated dUTP nick end-labeling positive cells increased following treatment with hyperoxia with or without chemotherapy.

Conclusions: Intermittent normobaric hyperoxia was found to be tumoricidal and thus may serve as an adjuvant therapy for lung cancer. Oxidative stress and its effects on DNA are increased following exposure to hyperoxia and even more with chemotherapy, and this may lead to apoptosis of lung tumors.

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Keywords: Apoptosis; Carboplatin; Hyperoxia; Lung neoplasms; Oxidative stress

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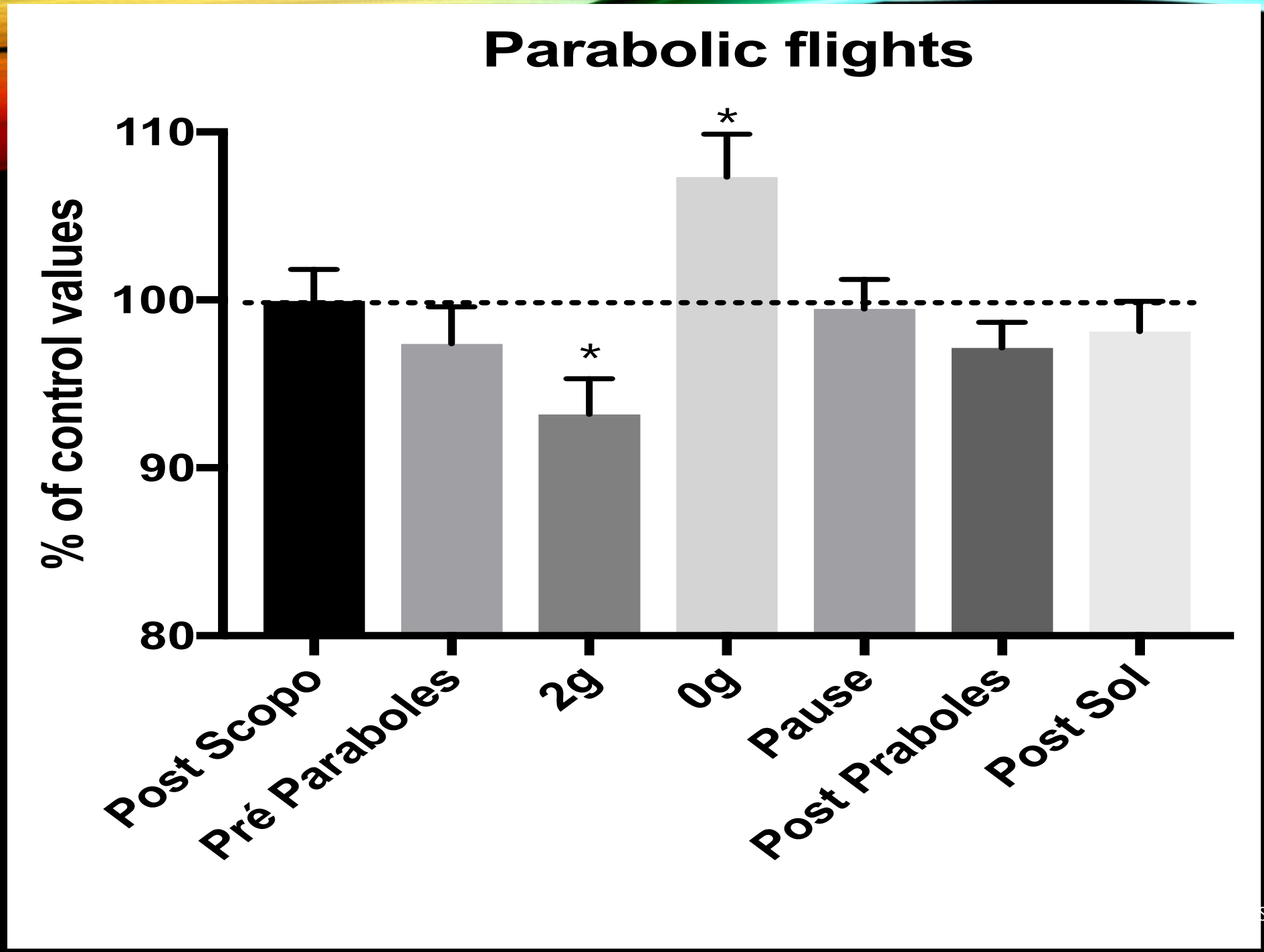
Parabolic flights
% of control values
110
100
90
80
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*
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Pré Paraboles
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Pause
Post Praboles
Post Sol

Functional comparison between critical flicker fusion frequency and simple cognitive tests in subjects breathing air or oxygen in normobaria

Walter Hemelryck, Miroslav Rozloznik, Peter Germonpré, Costantino Balestra and Pierre Lafère

Abstract

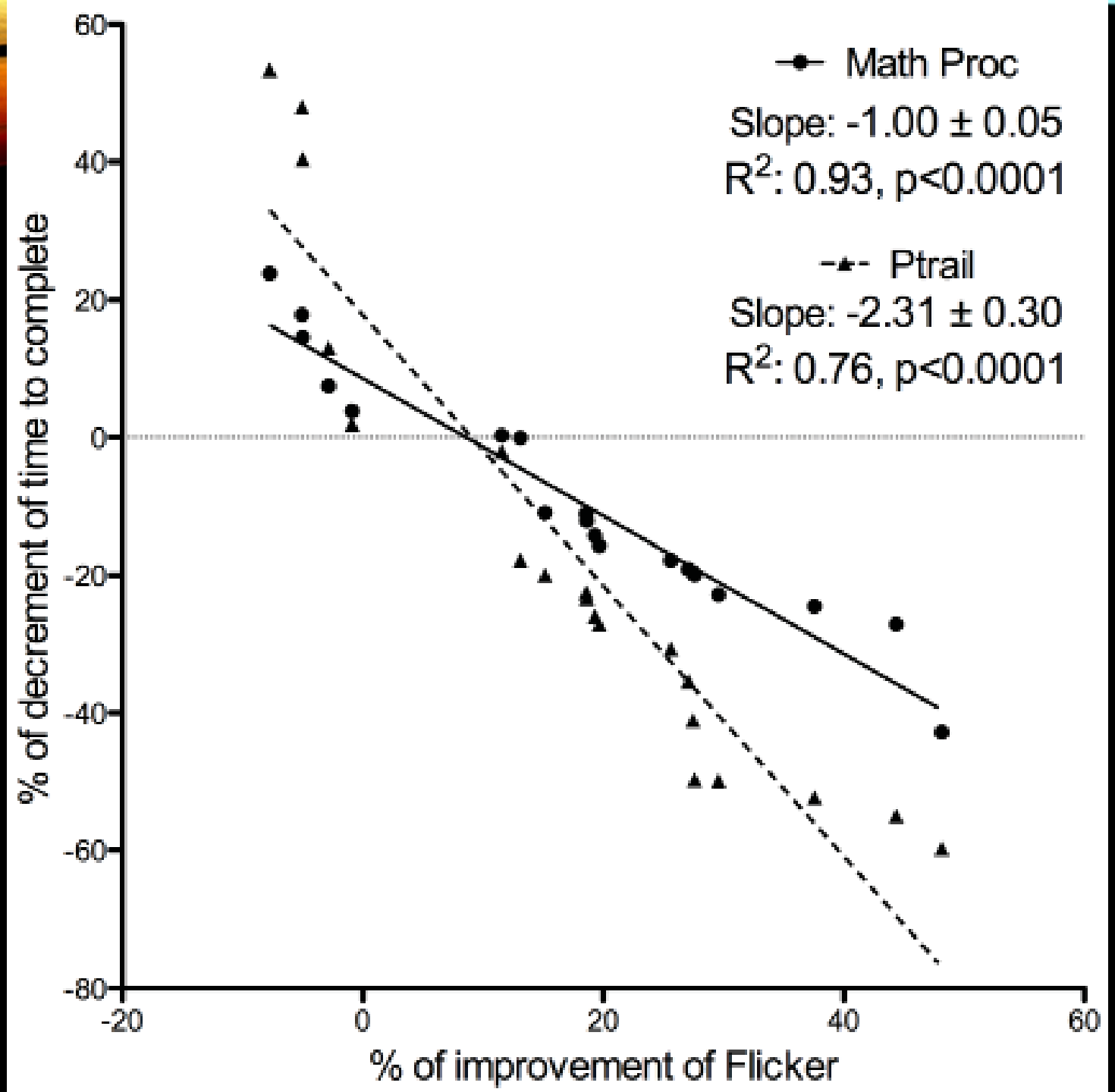
(Hemelryck W, Rozloznik M, Germonpré P, Balestra C, Lafère P. Functional comparison between critical flicker fusion frequency and simple cognitive tests in subjects breathing air or oxygen in normobaria. *Diving and Hyperbaric Medicine*. 2013 September;43(3):138-142.)

Introduction: Measurement of inert gas narcosis and its degree is difficult during operational circumstances, hence the need for a reliable, reproducible and adaptable tool. Although being an indirect measure of brain function, if reliable, critical flicker fusion frequency (CFFF) could address this need and be used for longitudinal studies on cortical arousal in humans.

Methods: To test the reliability of this method, the comparison between CFFF and three tests (Math-Processing Task, Trail-Making Task, and Perceptual Vigilance Task) from the Psychology Experiment Building Language battery (PEBL) were used to evaluate the effect of 10 minutes of 100% normobaric oxygen breathing on mental performance in 20 healthy male volunteers.

Results: Breathing normobaric oxygen significantly improved all but one of the measured parameters, with an increase of CFFF (117.3 ± 10.04% of baseline, $P < 0.0001$) and a significant reduction of time to complete in both the math-processing (2,103 ± 432.1 ms to 1,879 ± 417.5 ms, $P = 0.0091$) and trail-making tasks (1,992 ± 715.3 to 1,524 ± 527.8 ms, $P = 0.0241$). The magnitude of CFFF change and time to completion of both tests were inversely correlated (Pearson r = -0.9695 and -0.8731 respectively, $P < 0.0001$). The perceptual vigilance task did not show a difference between air and O_2 ($P > 0.4$).

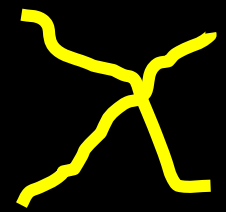
Conclusions: The CFFF test provides an assessment of cognitive function that is similar to some tests from PEBL, but requires a less complicated set up and could be used under various environmental conditions including diving. Further research is needed to assess the combined effects of increased pressure and variations in inspired gas mixtures during diving.

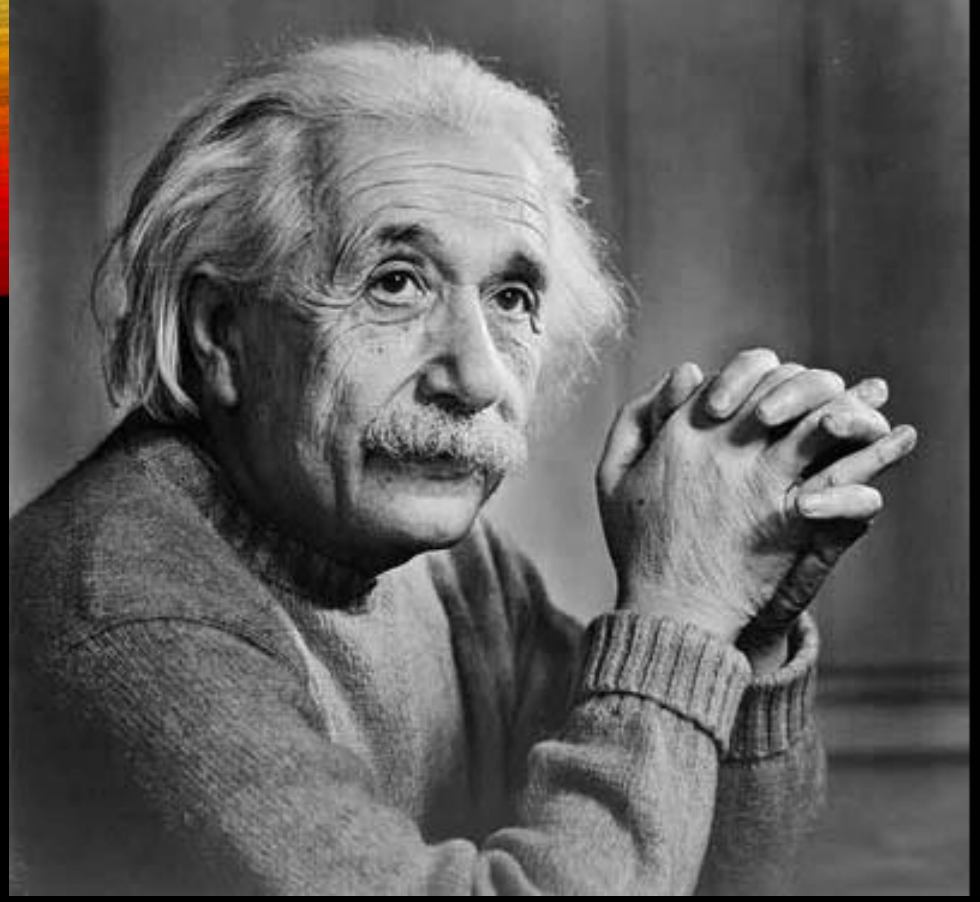

Math Proc
Slope: -1.00 ± 0.05
R2: 0.93, p<0.0001
Ptrail
Slope: -2.31 ± 0.30
R2: 0.76, p<0.0001
% of decrement of time to complete
% of improvement of Flicker
60
40
20
0
-20
-40
-60
-80
-20
0
20
40
60

NARCOSIS TEST

Are You Drunk ?

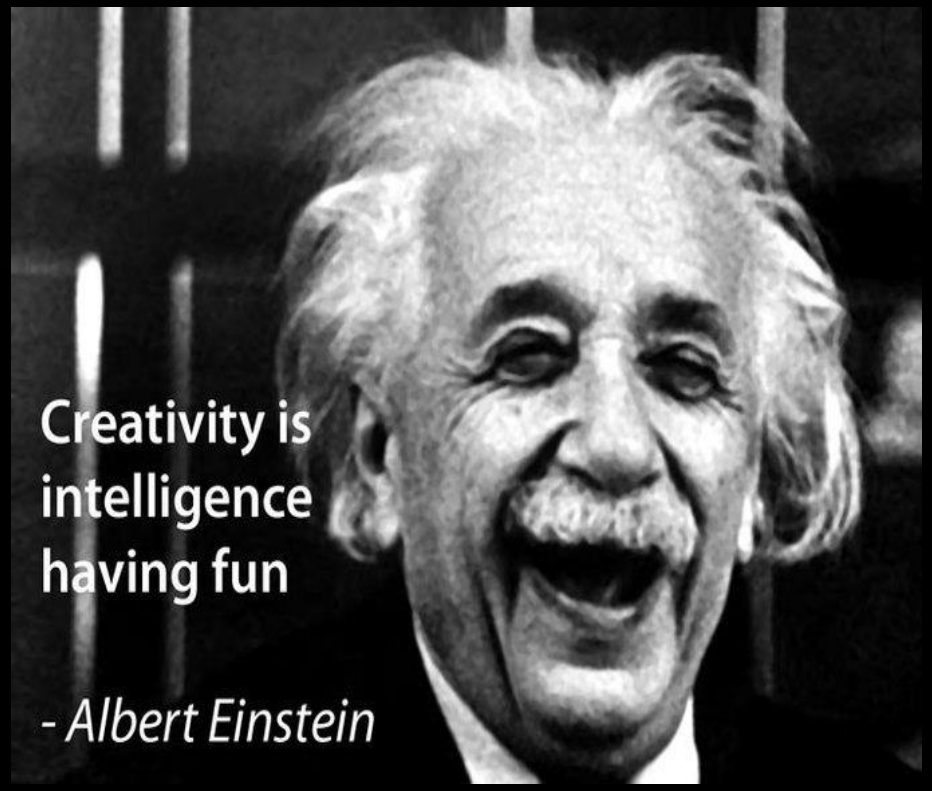
YES ☐ NO ☐





"Creativity is contagious,
pass it on"

- Albert Einstein



THINGS CAN ALWAYS GO WRONG EVEN WHIT FORESEEN EVENTS….


YOUR ATTENTION
I THANK YOU
FOR
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